REMARKS/ARGUMENTS

Claims 1-14 and 18-36 are active in this application, claims 15-17 and 37-40 having been cancelled.

Applicants' representative would like to thank Examiner Tentoni for the courteous and helpful discussion of the issues in the present application on February 9, 2009. The following remarks summarize and further expand on the content of that discussion.

The present invention relates to a method for electroblowing nanofibers comprising:

forcing a polymer fluid through a spinneret in a first direction towards a collector located a first distance from the spinneret, to form submicron sized nanofibers, while simultaneously blowing a gas through an orifice that is substantially concentrically arranged around the spinneret, wherein the gas is blown substantially in the first direction to contact the nanofibers;

wherein an electrostatic differential is generated between the spinneret and the collector; and

collecting the nanofibers;

wherein the polymer fluid comprises a member selected from the group consisting of hyaluronan, copolymers of hyaluronan and mixtures thereof.

The claims stand rejected under 35 U.S.C. 103 over Kim in view of Gravett. As acknowledged by the Examiner, Kim does not disclose the use of their process to produce hyaluronan fibers. In fact, Kim mentions only a handful of polymers useful in their process (see paragraph [0020] of Kim) none of which are biopolymers such as hyaluronan.

The Examiner has used the reference of Gravett to suggest the use of hyaluronan in the method of Kim. However, Gravett is not available as prior art against the present invention. Applicants note that previously during prosecution on February 21, 2006, Applicants filed a Declaration by Dufei Fang which established that Applicants invention was

conceived at least as early as August 2002, as noted by the submission of a research proposal to the US Army SBIR Program on August 14, 2002. As noted in the Declaration, the research proposal submitted to the SBIR program describes the invention sufficiently to show that the inventors had conceived the invention of combining electrospinning and melt blowing into a single process. Further, Applicants provide herewith patents issued from the applications mentioned at page 2 of the research proposal, which indicate biopolymers such as hyaluronic acid based polymers. Thus, Applicants have established an invention date at least as early as August 14, 2002.

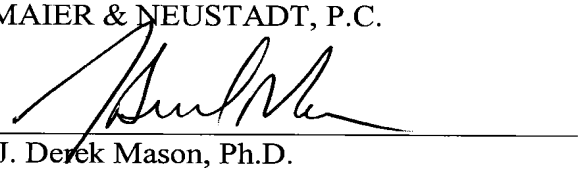
Gravett, on the other hand, was published July 29, 2004, after Applicants filing date of October 1, 2003, and thus is only capable of being applicable prior art under the provisions of 35 U.S.C. 102(a) or (e). Gravett can only be effective as prior art as of its earliest priority date of September 26, 2002, more than one month after the date of Applicants research proposal. Accordingly, Gravett is not available as prior art.

Without the Gravett reference, the Examiner's rejection for obviousness based on the combination of Kim and Gravett cannot stand and should be withdrawn.

As there are no other remaining rejections, Applicants submit that the application is now in condition for allowance and early notification of such action is earnestly solicited.

Respectfully submitted,

OBLON, SPIVAK, McCLELLAND,
MAIER & NEUSTADT, P.C.



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US006685956B2

(12) **United States Patent**
Chu et al.

(10) **Patent No.: US 6,685,956 B2**
(45) **Date of Patent: Feb. 3, 2004**

(54) **BIODEGRADABLE AND/OR BIOABSORBABLE FIBROUS ARTICLES AND METHODS FOR USING THE ARTICLES FOR MEDICAL APPLICATIONS**

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(73) Assignee: **The Research Foundation at State University of New York**, Stony Brook, NY (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 88 days.

(21) Appl. No.: **09/859,007**

(22) Filed: **May 16, 2001**

(65) **Prior Publication Data**

US 2002/0173213 A1 Nov. 21, 2002

(51) **Int. Cl.**[7] **A61F 2/02**

(52) **U.S. Cl.** **424/423**; 424/424; 424/425; 424/426

(58) **Field of Search** 424/423, 424, 424/425, 426

(56) **References Cited**

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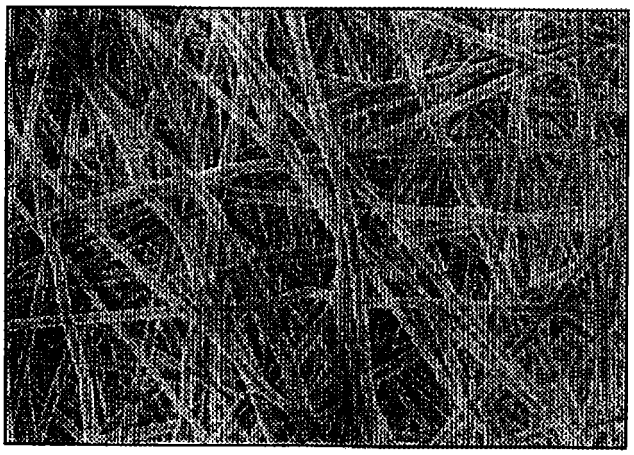
Primary Examiner—Carlos Azpuru
(74) *Attorney, Agent, or Firm*—Hoffmann & Baron, LLP

(57) **ABSTRACT**

Biodegradable and/or bioabsorable fibrous articles and methods for using the articles in medical applications are disclosed. The biodegradable and/or bioabsorable fibrous articles, which are formed by elctrospinning fibers of biodegradable and/or bioabsorbable fiberizable material, comprise a composite (or asymmetric composite) of different biodegradable and/or bioabsorbable fibers. Articles having specific medical uses include an adhesion-reducing barrier and a controlled delivery system. The methods include methods for reducing surgical adhesions, controlled delivery of a medicinal agent and providing controlled tissue healing.

24 Claims, 14 Drawing Sheets



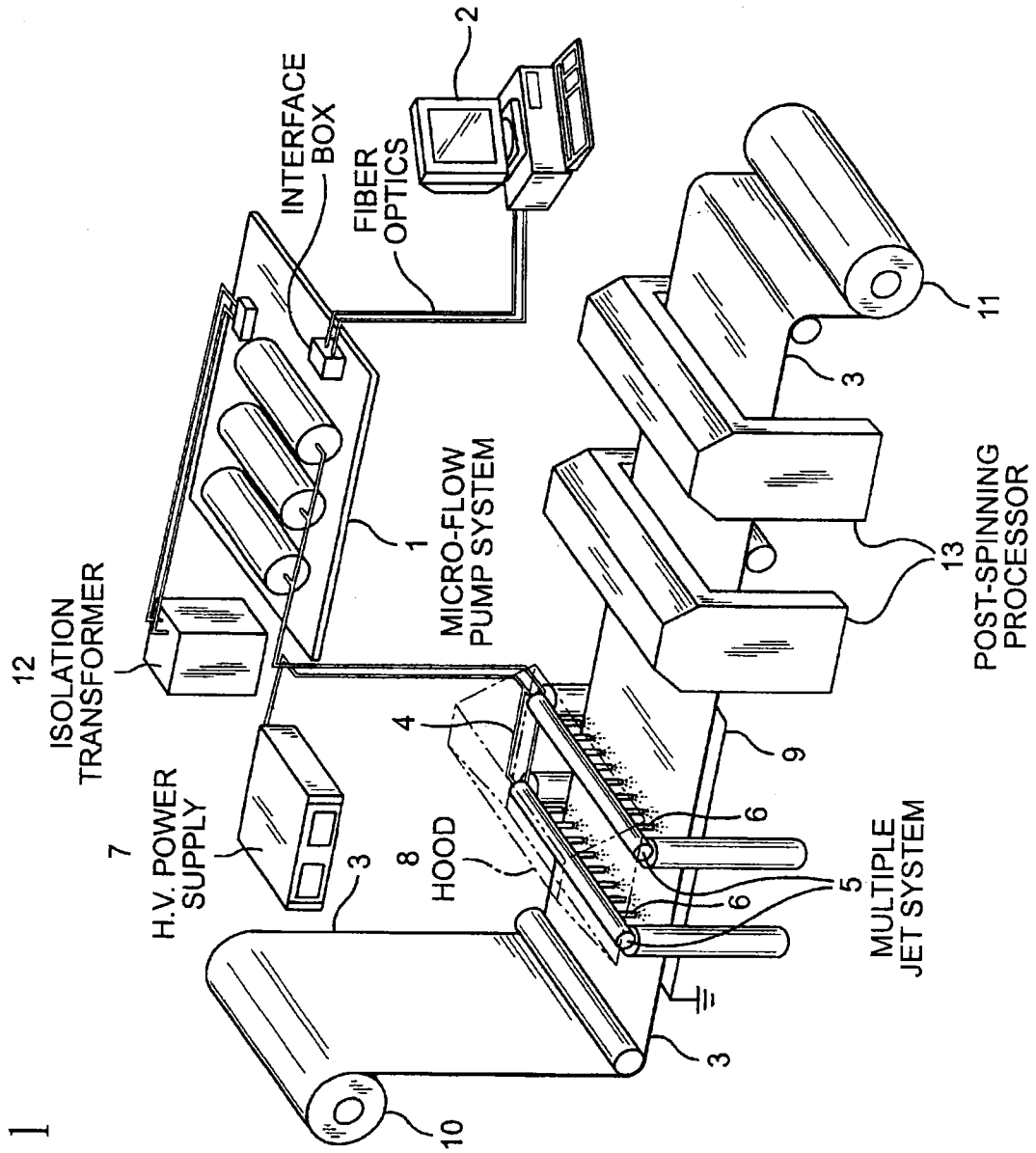

2
INTERFACE BOX
FIBER OPTICS
1
MICRO-FLOW PUMP SYSTEM
12
ISOLATION TRANSFORMER
7
H.V. POWER SUPPLY
3
8
HOOD
4
6
5
MULTIPLE JET SYSTEM
9
10
3
3
11
13
POST-SPINNING PROCESSOR

FIG. 1

FIG. 2 (a)

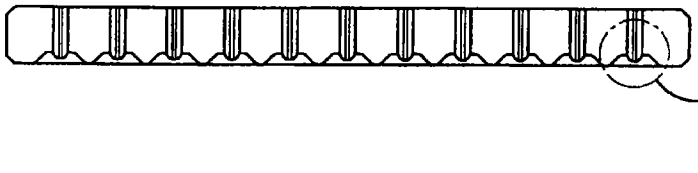


FIG. 2 (b)

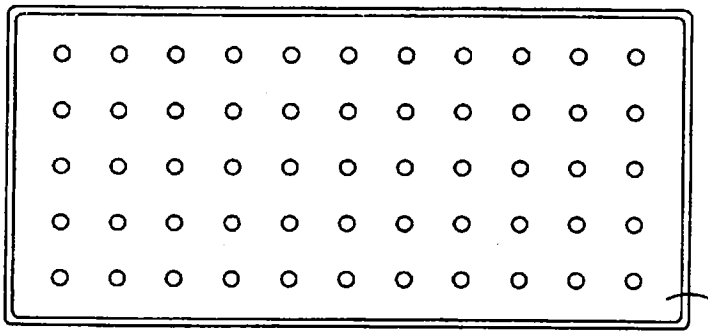


FIG. 2 (c)

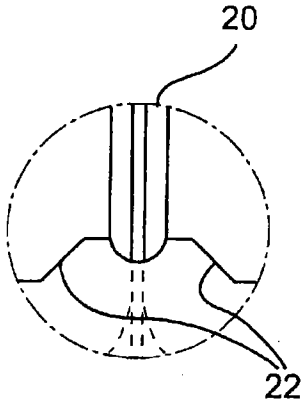


FIG. 3 (a)

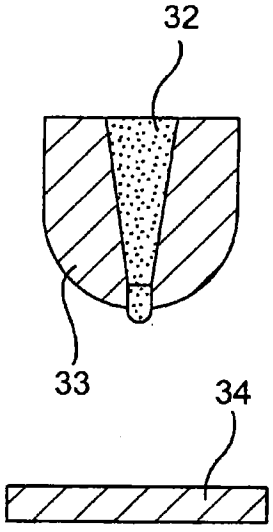


FIG. 3 (b)

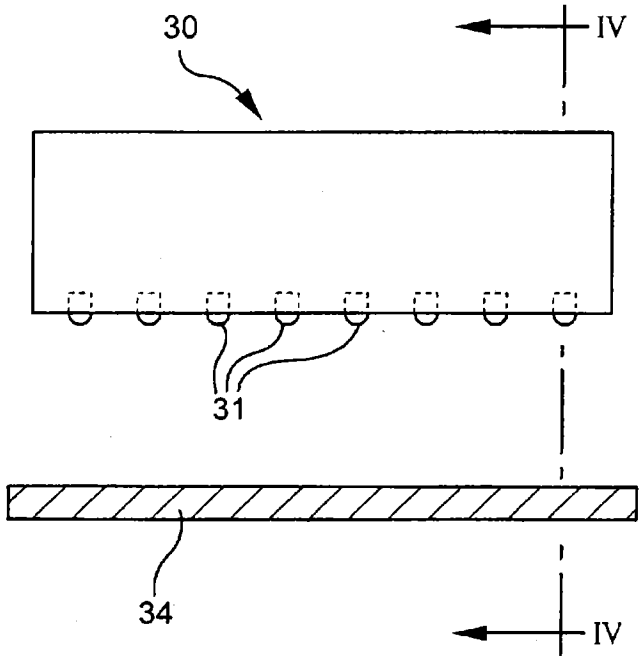


FIG. 3 (c)

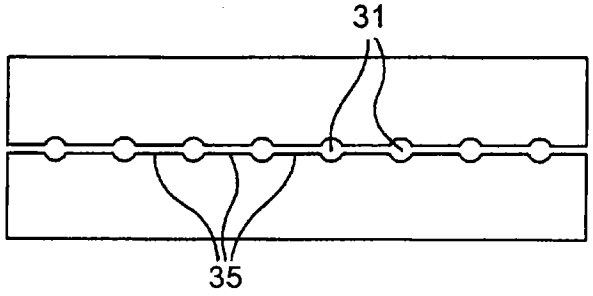


FIG. 4 SPUN MEMBRANE WITH 1 WT% KH_2PO_4

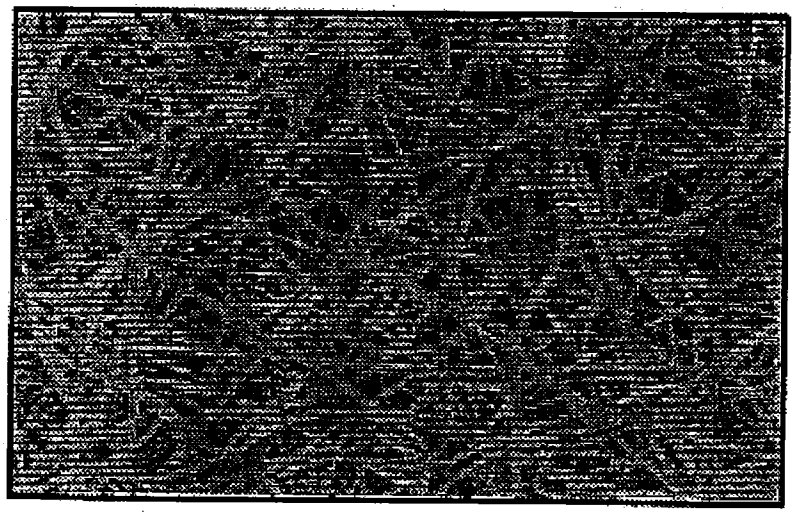


FIG. 5 SPUN MEMBRANE WITHOUT SALT

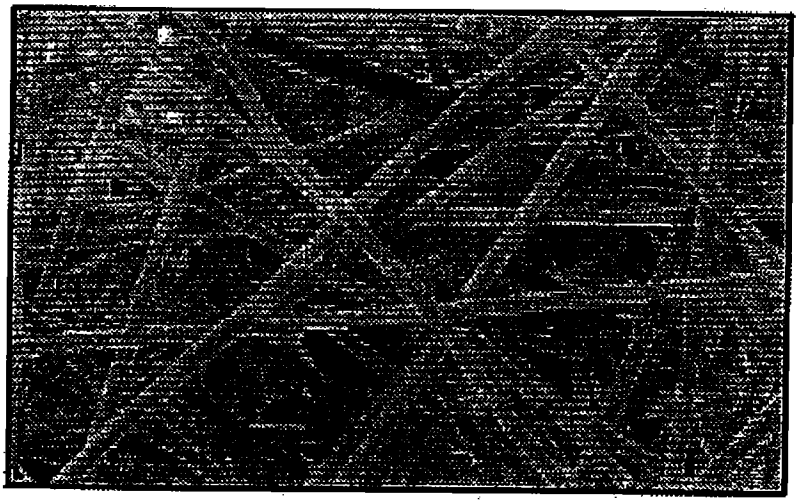


FIG. 6

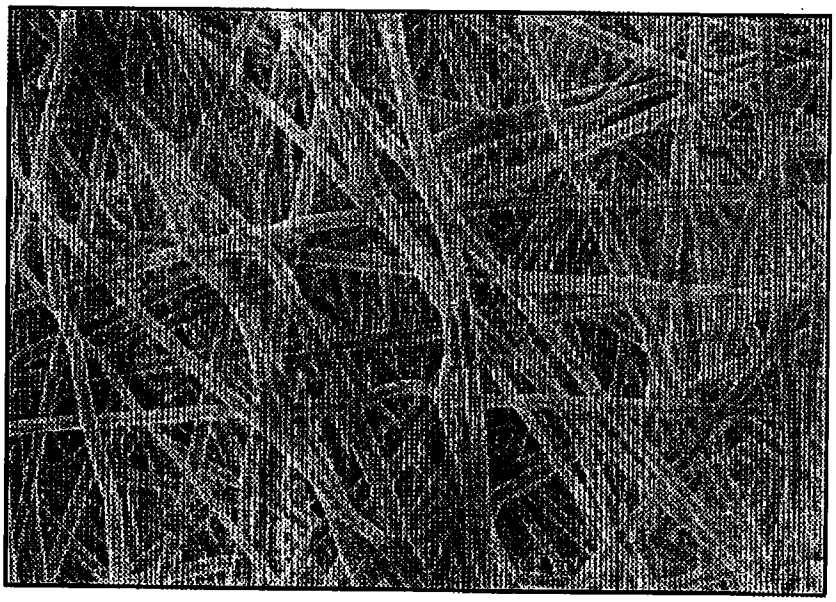


FIG. 7

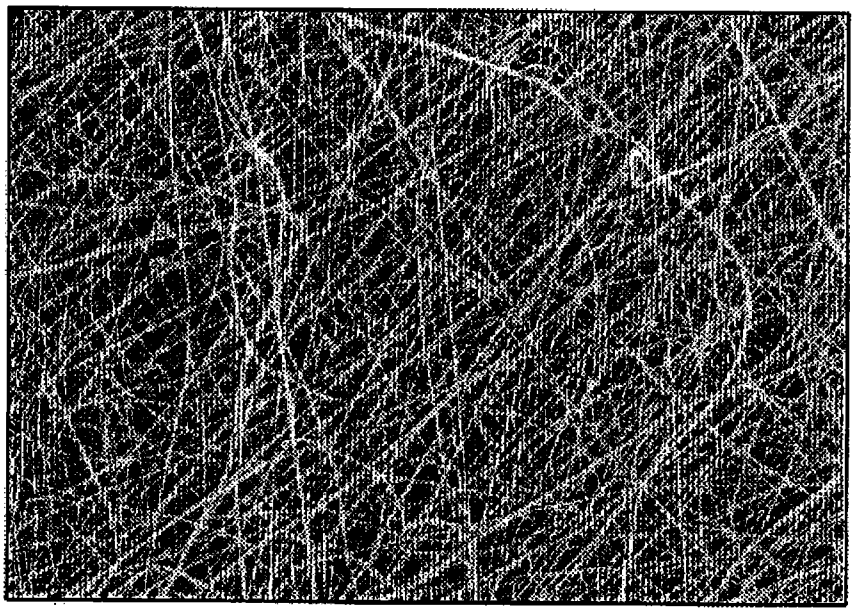


FIG. 8 IN VITRO DRUG RELEASE PROFILE

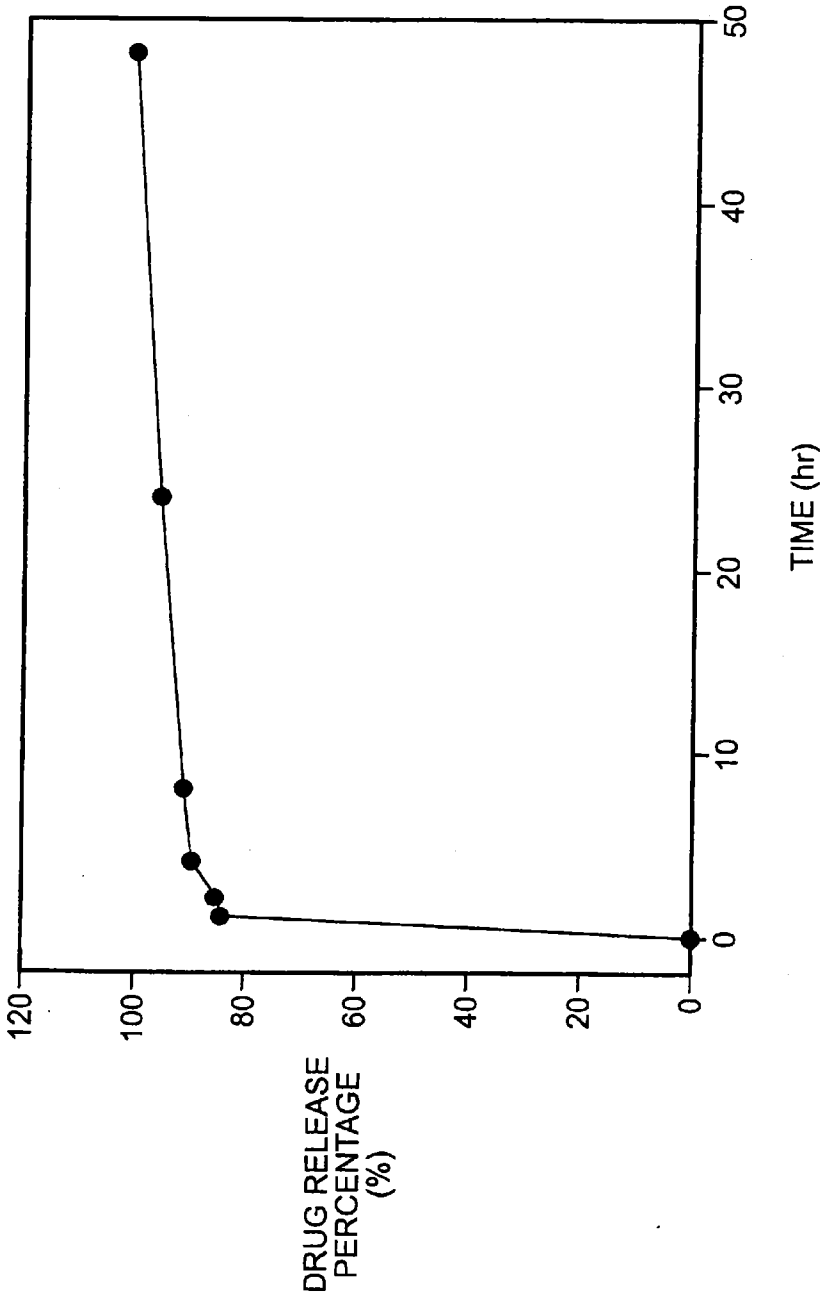


FIG. 9 SEM IMAGE OF ELECTROSPUN PLA MEMBRANE

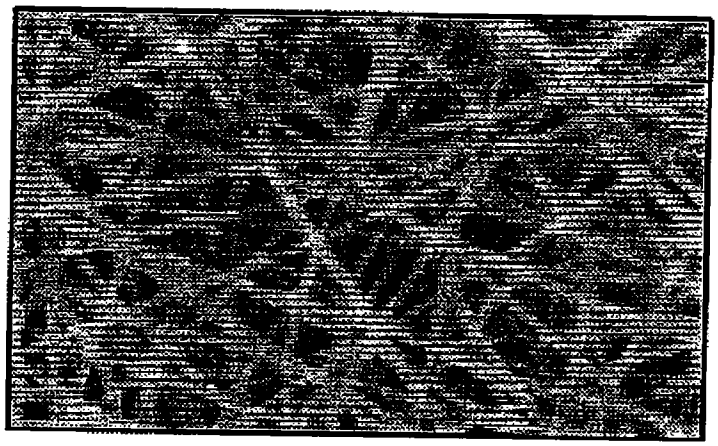
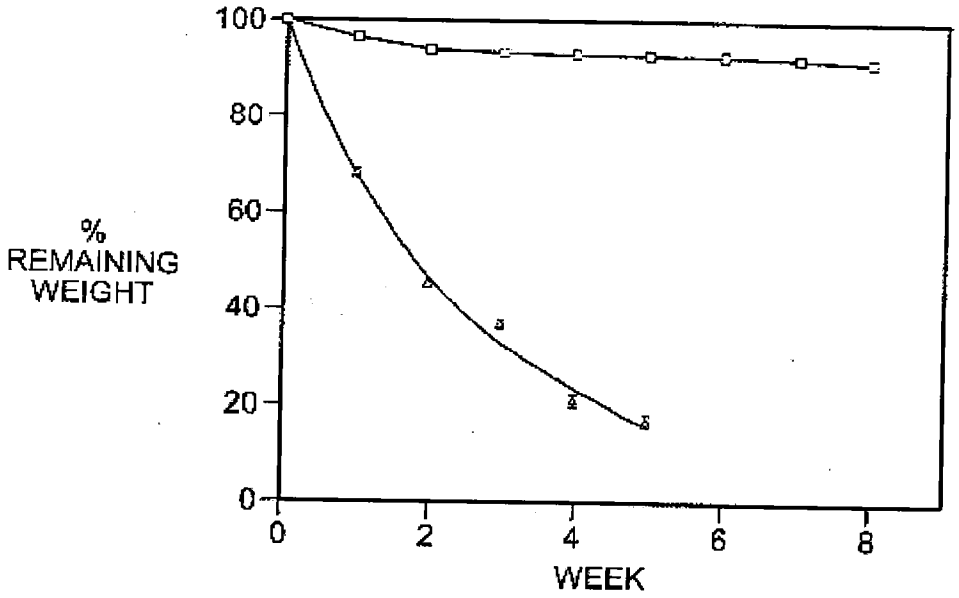


FIG. 10 BIODEGRADATION RATE OF ELECTROSPUN MEMBRANE



▵ AMORPHOUS PGA FILM
▫ P(DL)LA ELECTROSPUN FILM

FIG. 11 DUEL THICKNESS PLA MEMBRANE

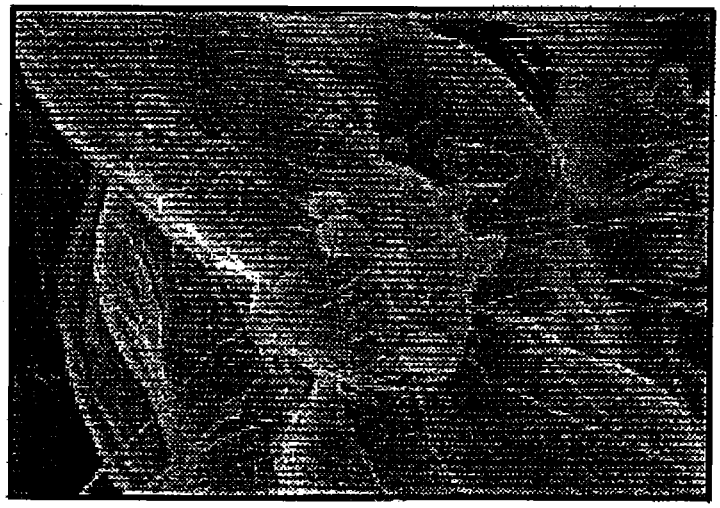


FIG. 12 MEMBRANE AFTER 1 WEEK OF DEGRADATION

FIG. 13 INCIDENCE OF ADHESION

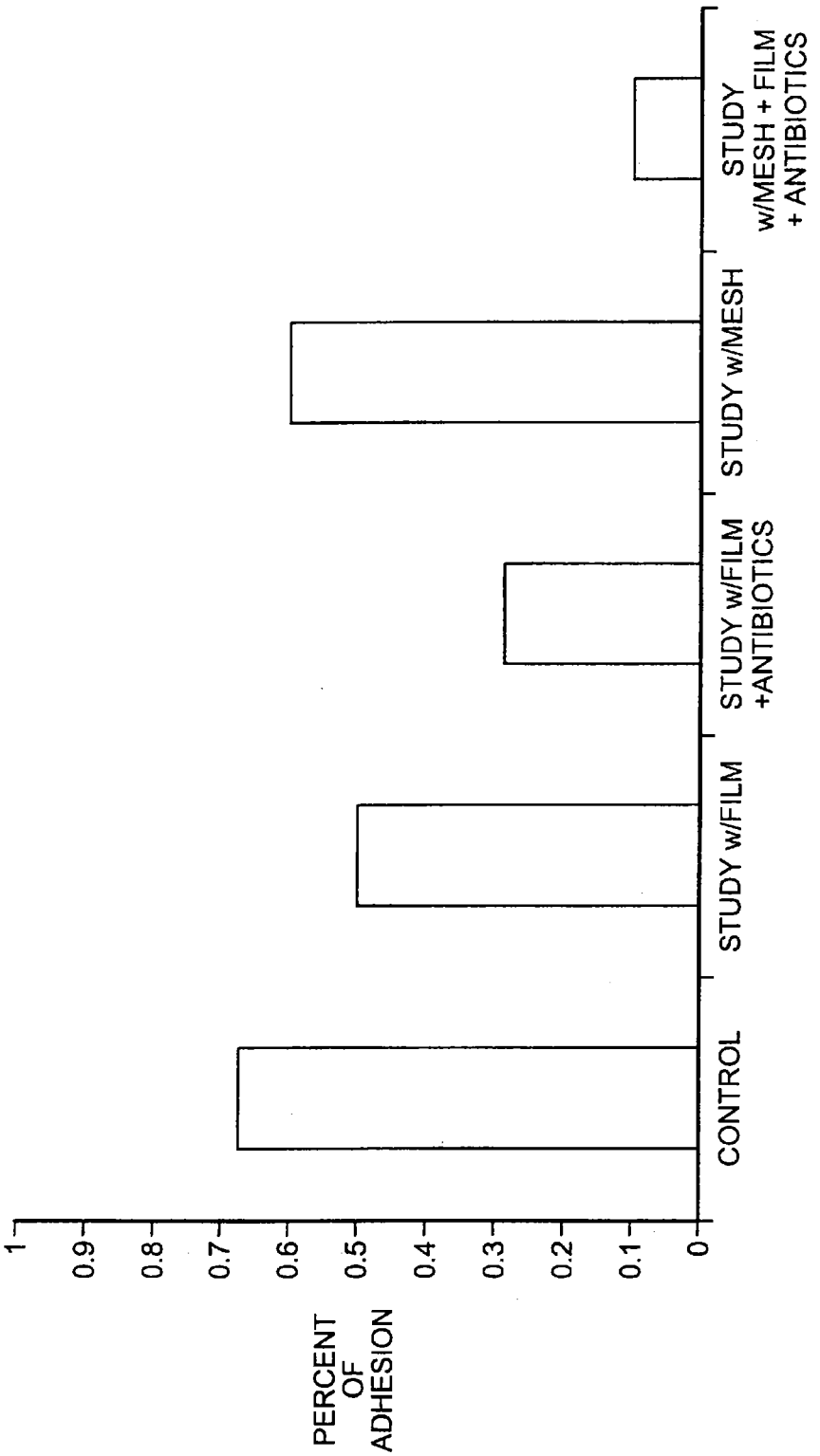


FIG. 14 CECAL ADHESION TENSION (N)

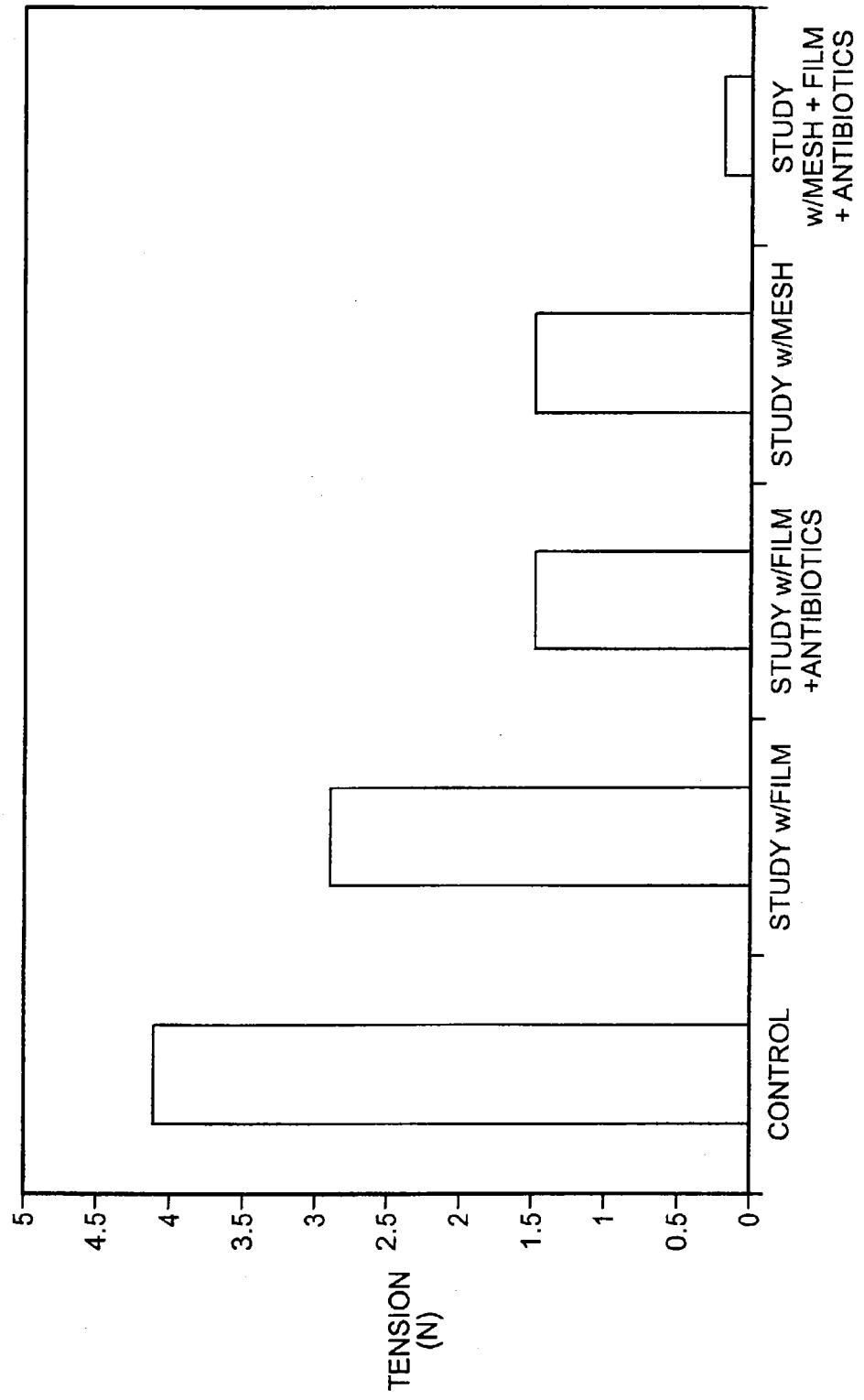


FIG. 15 ANTIBACTERIAL TEST RESULTS OF PLA MEMBRANE

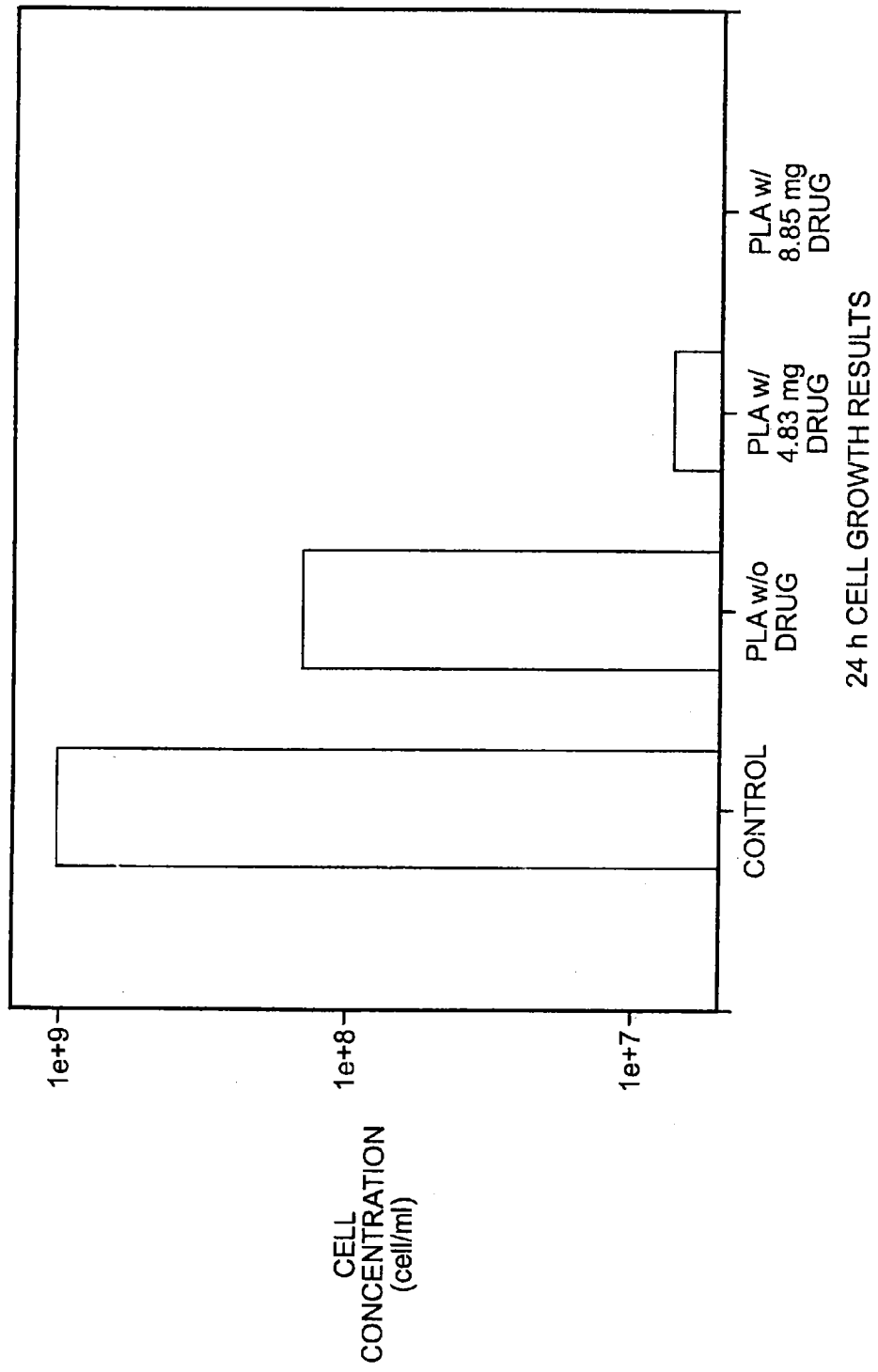


FIG. 16 SEM IMAGE OF AS-SPUN MEMBRANE

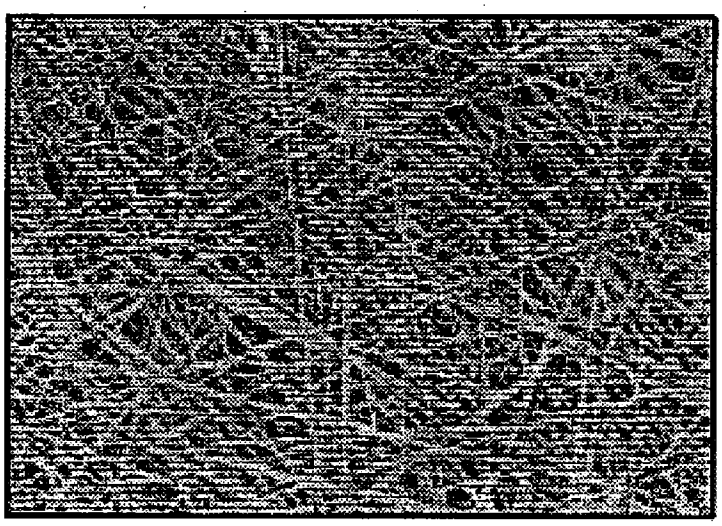
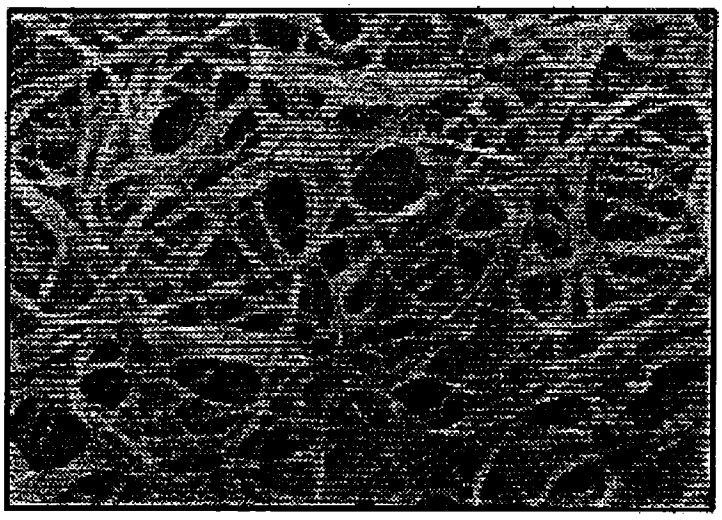


FIG. 17 *IN-VIVO* DEGRADATION AFTER A WEEK



BIODEGRADABLE AND/OR BIOABSORBABLE FIBROUS ARTICLES AND METHODS FOR USING THE ARTICLES FOR MEDICAL APPLICATIONS

BACKGROUND OF INVENTION

The present invention relates to biodegradable and/or bioabsorbable fibrous articles. More specifically, the present invention is directed to products and methods having utility in medical applications. In one embodiment, the fibrous articles of the invention are polymeric membranes.

Polymeric membranes produced by an electrospinning technique have been suggested as being useful for biological membranes such as substrates for immobilized enzymes and catalyst systems, wound dressing materials and artificial blood vessels, as well as for aerosol filters and ballistic garments.

Electrospinning is an atomization process of a conducting fluid which exploits the interactions between an electrostatic field and the conducting fluid. When an external electrostatic field is applied to a conducting fluid (e.g., a semi-dilute polymer solution or a polymer melt), a suspended conical droplet is formed, whereby the surface tension of the droplet is in equilibrium with the electric field. Electrostatic atomization occurs when the electrostatic field is strong enough to overcome the surface tension of the liquid. The liquid droplet then becomes unstable and a tiny jet is ejected from the surface of the droplet. As it reaches a grounded target, the material can be collected as an interconnected web containing relatively fine, i.e. small diameter, fibers. The resulting films (or membranes) from these small diameter fibers have very large surface area to volume ratios and small pore sizes. However, no practical industrial process has been implemented for producing membranes useful for medical applications. This is because with the production of small fibers, such as nanosize fibers, the total yield of the process is very low and a scale-up process, which maintains the performance characteristics of the films (or membranes), cannot be easily achieved.

U.S. Pat. No. 4,323,525 is directed to a process for the production of tubular products by electrostatically spinning a liquid containing a fiber-forming material. The process involves introducing the liquid into an electric field through a nozzle, under conditions to produce fibers of the fiber-forming material, which tend to be drawn to a charged collector, and collecting the fibers on a charged tubular collector which rotates about its longitudinal axis, to form the fiberous tubular product. It is also disclosed that several nozzles can be used to increase the rate of fiber production. However, there is no suggestion or teaching of how to control the physical characteristics of the tubular product, other than by controlling the charge and rotation speed of the tubular collector. It is further noted that the spinning process of the '525 patent is used to fabricate tubular products having a homogenous fiber matrix across the wall thickness.

U.S. Pat. No. 4,689,186 is directed to a process for the production of polyurethane tubular products by electrostatically spinning a fiber-forming liquid containing the polyurethane. It is disclosed that auxiliary electrodes can be placed around the collector to help facilitate collection of the fibers. It is disclosed that the auxiliary electrodes can be arranged to facilitate separation or to prevent adhesion of the formed fibers. There is no teaching or suggestion of independently controlling jet formation, jet acceleration and fiber collection. It is also noted that the spinning process of the '186 patent is used to fabricate tubular products having a homogenous fiber matrix across the wall thickness.

In one aspect, the present invention is directed to products and methods for preventing the formation of post-surgical adhesions between a healing trauma site and adjacent surrounding tissue.

Adhesion formation is a natural and inevitable consequence of surgery. Injury, surgical incisions, abrasion or other operative damage to the peritoneum, pleural or abdominal cavity results in an outpouring of a serosanguinous exudate. This exudate can accumulate on the injured surface and subsequently coagulate, producing fibrinous bands between abutting surfaces which can become organized by fibroblast proliferation to become collagenous adhesions. Adhesions are also known to form at bone fracture sites resulting in adhesions between the bone fracture surface and the surrounding tissue.

Adhesions can lead to serious complications. For example, adhesions that form in relation to intestinal surgery such as bowel resection, hernia repair, etc., may cause obstruction of the intestine. Adhesions that form near a bone fracture site may reduce or hinder the normal movement of the area of repair by restricting the natural movement of tendons over the adjacent bone. Adhesions may also form in the vicinity of nerves and disrupt nerve transmissions with a resultant diminution of sensory or motor function. Adhesions have also been known to lead to female infertility, chronic debilitating pain and difficulty with future operations. Typically, a patient will often have to undergo additional surgery to remove adhesions, only to have them reform.

Various methods and substances have been used in the hope of preventing post-operative adhesions. Certain drugs and surfactants have been suggested. For example, U.S. Pat. No. 4,911,926 is directed to adhesion prevention by application of aqueous and non-aqueous compositions of a polyoxyalkylene block copolymer to injured areas of the peritoneal or pleural cavity or organs situated therein subsequent to surgical injury.

Other surgical adjuvants have been used in an attempt to minimize or prevent adhesions following surgery, including anti-inflammatory drugs (such as corticosteroids) to decrease vascular permeability, antihistamines to reduce fibroblast proliferation, anticoagulants (such as heparin) and antibiotics (such as vibramycin or metokin) to reduce the incidence of infection. However, the use of drugs or compositions which are applied to the surgical area have only had limited success in preventing adhesions.

Another approach to adhesion prevention involves application of a physical barrier at the area of surgical injury. The theory is that a mechanical barrier, placed between the injured, healing serosal surfaces, which persists until all serosal healing has taken place will prevent adhesions and the sequela, e.g., small bowel obstruction. Bioabsorbable materials in the form of barrier layers to prevent adhesions of tissues which have been suggested include products based on cellulose materials. However, the use of commercial cellulose based products to prevent adhesions has certain drawbacks. For example, the performance in preventing adhesions is limited. Furthermore, certain products have been reported to have handling problems during surgery or can cause scars after use.

U.S. Pat. No. 4,674,488 is directed to interposing a barrier layer of soft biological tissue, such as collagen, collagen-fabric films, collagen membranes, or reconstituted collagen or Dacron™, mesh, at the interface of a bone fracture and the

surrounding tissue. U.S. Pat. No. 4,603,695 is directed to a molded polymeric material for preventing adhesion of vital tissues. The polymeric material is made of a biodegradable and absorbable polymer such as certain polyesters, collagen, amino acid polymers and chitin and may be placed where there is a possibility of adhesion setting in. Although biological materials, such as collagen, are generally "biocompatible," they can generate scars when implanted in certain forms, and it is difficult to precisely control the degradation of such materials.

Other materials have also been used to form physical barriers in an attempt to prevent adhesions, including silicone elastomers, gelatin films and knit fabrics of oxidized regenerated cellulose (hereinafter ORC). In some cases, it is suggested that heparin, heparinoid, or hexuronyl hexosaminogly can be incorporated into the matrix of an ORC fabric or other matrices of hyaluronic acid, cross-linked and uncross-linked collagen webs, synthetic resorbable polymers, gelatin films, absorbable gel films, oxidized cellulose fabrics and films which are fabricated into a form that is said to be drapable, conformable and adherent to body organs and substantially absorbable within 30 days. See, e.g., U.S. Pat. No. 4,840,626 or EPA Publication No. 0 262 890 or EPA Publication No. 0 372 969. However, as discussed above, it is difficult to precisely control the degradation rate of many of these materials and scar tissue can result from use of many of the materials.

Physical barriers are also used to cover and protect wound sites. PCT/US91/08972 is directed to a surgical article having a bioabsorbable fibrous matrix in a laminar relationship with a bioabsorbable cell barrier sheet. U.S. Pat. No. 5,092,884 and EPA Publication No. 0 334 046 are directed to a surgical composite structure having absorbable and non-absorbable components which may be useful for repairing anatomical defects, e.g., preventing hernia formation in an infected area. The nonabsorbable portion of the composite acts as a reinforcement material. The growth of natural tissue is said to be enhanced by controlled degradation of the absorbable portion. U.S. Pat. No. 5,035,893 relates to a wound covering composition having a sheet of biopolymeric material and a film of polyurethane resin. An antibacterial agent may be provided between the polyurethane film and the sheet of biopolymeric material, thereby forming a three-layer wound covering material. With the cure of the wound, it is said that the biopolymeric material is taken in as living tissue and the polyurethane film can be peeled off from the sheet without hurting the surface of a wound. Again, the use of many biopolymeric materials can result in the formation of scar tissue.

Thus, there is a need for improved membranes and other fibrous articles, which can be produced on an industrial scale, and for improved products and methods for reducing the formation of post-surgical adhesions, as well as for other medical applications, which do not have the above-mentioned disadvantages.

SUMMARY OF INVENTION

According to the present invention, it has now been found that biodegradable and/or bioabsorbable articles, e.g. membranes, having improved performance and handling characteristics for medical applications can be provided without the above-mentioned disadvantages.

In one aspect, the invention relates to a biodegradable and/or bioabsorbable fibrous article formed by electrospinning fibers of biodegradable and/or bioabsorbable fiberizable material, in which the article contains a composite of different biodegradable and/or bioabsorbable fibers.

In another aspect, the invention relates to a biodegradable and/or bioabsorbable fibrous article formed by electrospinning fibers of biodegradable and/or bioabsorbable fiberizable material, in which the article contains an asymmetric composite of different biodegradable and/or bioabsorbable fibers.

Different fibers can include fibers of different diameters, fibers of different biodegradable and/or bioabsorbable materials, or fibers of both different diameters and different biodegradable and/or bioabsorbable materials.

Preferably, the article will contain at least about 20 weight percent of submicron diameter fibers, more preferably, the article will contain at least about 50 weight percent of submicron diameter fibers.

Preferably, the biodegradable and/or bioabsorbable fiberizable material is a biodegradable and/or bioabsorbable polymer. The biodegradable and/or bioabsorbable polymer preferably contains a monomer selected from the group consisting of a glycolide, lactide, dioxanone, caprolactone, trimethylene carbonate, ethylene glycol and lysine.

In one embodiment the biodegradable and/or bioabsorbable polymer contains a biodegradable and/or bioabsorbable linear aliphatic polyester, more preferably a polyglycolide or a poly(glycolide-co-lactide) copolymer.

In another embodiment the biodegradable and/or bioabsorbable fiberizable material contains a material derived from biological tissue, e.g., collagen, gelatin, polypeptides, proteins, hyaluronan acid and derivatives or synthetic biopolymers.

The fibers of different biodegradable and/or bioabsorbable materials can include fibers having different chemical composition, such as different polymeric materials, different molecular weights of the same polymeric material, different blends of polymers, materials having different additives or materials having different concentration of additives.

In another embodiment the article will contain different fibers, i.e. different diameters and/or different materials, having diameters in the range from a few nanometers up to almost about one micron, more preferably about 10 up to about 1000 nanometers and most preferably from about 20 to about 500 nanometers. The fibers of different diameters can include both fibers having diameters less than 300 nanometers and fibers having diameters greater than 300 nanometers.

The article can also contain small blobs of biodegradable and/or bioabsorbable material. Preferably, the small blobs will have diameters in the range of about 20 to about 500 nanometers and, more preferably, about 200 to about 1500 nanometers.

In one embodiment, the article also contains at least one medicinal agent. The medicinal agent can be contained within the biodegradable and/or bioabsorbable material itself, including within the fibers or within the small blobs of material, if present. In such a case, the fibers (and/or small blobs) can contain different concentrations of the medicinal agent or different medicinal agents.

The article can also have the structure of a plurality of layers, wherein at least one of the layers is a composite (or asymmetric composite) of different biodegradable and/or bioabsorbable fibers. In such a case, the article can also contain at least one medicinal agent between at least two of the layers.

In one embodiment, the above described fibrous articles are in the form of a membrane.

The membrane according to the invention will preferably have a thickness in the range of about 10 to about 5000 microns, more preferably about 20 to about 1000 microns.

In another aspect, the invention relates to a fibrous article formed by electrospinning different fibers of different materials, in which the article contains a composite of different fibers containing fibers of at least one biodegradable material and fibers of at least one non-biodegradable material. Preferably, the compositite of different fibers will contain submicron diameter fibers. The composite can be an asymmetric composite.

In another aspect, the invention is directed towards an adhesion-reducing barrier containing a biodegradable and/or bioabsorbable membrane, in which the membrane contains:

a composite of different biodegradable and/or bioabsorbable fibers; or

an asymmetric composite of different biodegradable and/or bioabsorbable fibers.

Preferably, the adhesion-reducing barrier contains the above described membranes.

In yet another aspect, the invention is directed to a method for reducing surgical adhesions which involves positioning an adhesion-reducing barrier between the site of surgical activity and neighboring tissues. The barrier contains a biodegradable and/or bioabsorbable membrane, in which the membrane contains:

a composite (or an asymmetric composite) of different biodegradable and/or bioabsorbable fibers;

a plurality of layers, with at least two layers having different biodegradable and/or bioabsorbable fibers from each other; or

sub-micron diameter biodegradable and/or bioabsorbable fibers, having at least one medicinal agent contained within the fibers.

Preferably, the method involves use of the above described barriers.

In yet another aspect, the invention is directed to a system for controlled delivery of a medicinal agent which contains the medicinal agent to be delivered and a biodegradable and/or bioabsorbable fibrous article physically associated with the medicinal agent to release the agent at a controlled rate. The article contains a composite of different biodegradable and/or bioabsorbable fibers or an asymmetric composite of different biodegradable and/or bioabsorbable fibers.

Preferably, the system will include the articles and biodegradable and/or bioabsorbable materials discussed above.

In another aspect, the invention is directed to a method for the controlled delivery of a medicinal agent which involves implanting at a target site in an animal, a system for controlled delivery of a medicinal agent. The system for controlled delivery of a medicinal agent contains the medicinal agent to be delivered and a biodegradable and/or bioabsorbable fibrous article physically associated with the medicinal agent to release the agent at a controlled rate. The article contains a composite of different biodegradable and/or bioabsorbable fibers or an asymmetric composite of different biodegradable and/or bioabsorbable fibers.

Preferably, the method involves use of the above described system.

The present invention provides biodegradable and/or bioabsorbable fibrous articles, e.g. membranes, having improved performance and handling characteristics for medical applications, including improved performance in preventing adhesions. The invention also provides fibrous articles containing fibers of controlled size and having controlled morphology and biodegradation rate with utility in a controlled delivery system.

Additional objects, advantages and novel features of the invention will be set forth in part in the description and examples which follow, and in part will become apparent to those skilled in the art upon examination of the following, or may be learned by practice of the invention. The objects and advantages of the invention may be realized and attained by means of the instrumentalities and combinations particularly pointed out in the appended claims.

BRIEF DESCRIPTION OF THE FIGURES

FIG. **1** is a schematic of an electrospinning system.

FIG. **2** is a schematic of an array of spinnerets for an electrospinning process.

FIG. **3**(*a*) is a side view schematic of a multiple spinneret system for producing membranes in accordance with the invention.

FIG. **3**(*b*) is a cross-sectional view of the spinneret system of FIG. **3**(*a*) as seen along viewing lines IV—IV thereof.

FIG. **3**(*c*) is a bottom view of the multiple spinneret system of FIG. **3**(*a*).

FIG. **4** is an SEM of a PLA-co-PGA membrane spun from a solution containing 1 wt % KH_2PO_4.

FIG. **5** is an SEM of a PLA-co-PGA membrane spun from a solution without salt added.

FIG. **6** is an SEM of a membrane described in Example 1.

FIG. **7** is an SEM of a membrane described in Example 4.

FIG. **8** is a graph of the results of the drug release test described in Example 4.

FIG. **9** is an SEM of a PLA membrane described in Example 5.

FIG. **10** is a graph of the results of the biodegradation tests described in Example 6.

FIG. **11** is an SEM of the PLA membrane described in Example 7.

FIG. **12** is an SEM of the PLA membrane described in Example 7 after 1 week of degradation.

FIG. **13** is a graph of the results of the adhesion experiment described in Example 8.

FIG. **14** is a graph showing the tensiometer readings from the experiment described in Example 8.

FIG. **15** is a graph of the results of the antibacterial test described in Example 9.

FIG. **16** is an SEM of the as spun membrane described in Example 10.

FIG. **17** is an SEM of the partially biodegraded membrane described in Example 10.

DETAILED DESCRIPTION OF THE INVENTION

The present invention is directed to biodegradable and/or bioabsorbable fibrous articles and methods for using the articles for medical applications including reducing the formation of post-surgical adhesions between a healing trauma site and the adjacent tissue and controlled delivery systems.

In one aspect, the invention relates to a biodegradable and bioabsorbable fibrous article formed by electrospinning fibers of biodegradable and/or bioabsorbable fiberizable material in which the article contains a composite of different biodegradable and/or bioabsorbable fibers.

In another aspect, the article can contain an asymmetric composite of different biodegradable and/or bioabsorbable fibers.

In yet another aspect, the article can also include fibers of at least one non-biodegradable/non-bioabsorbable material.

By the term biodegradable is intended a material which is broken down (usually gradually) by the body of an animal, e.g. a mammal, after implantation.

By the term bioabsorbable is intended a material which is absorbed or resorbed by the body of an animal, e.g. a mammal, after implantation, such that the material eventually becomes essentially non-detectable at the site of implantation.

By the terminology "biodegradable and/or bioabsorbable fiberizable material" is intended any material which is biocompatible, as well as biodegradable and/or bioabsorbable, and capable of being formed into fibers, as described more fully below. The material is also capable of being formed into a fibrous article which is suitable for implantation into an animal and capable of being biodegraded and/or bioabsorbed by the animal.

The biodegradable and/or bioabsorbable fiberizable material is preferably a biodegradable and bioabsorbable polymer. Examples of suitable polymers can be found in Bezwada, Rao S. et al. (1997) *Poly(p-Dioxanone) and its copolymers, in Handbook of Biodegradable Polymers,* A. J. Domb, J. Kost and D. M. Wiseman, editors, Hardwood Academic Publishers, The Netherlands, pp. 29–61, the disclosure of which is incorporated herein by reference in its entirety.

In a preferred embodiment the biodegradable and/or bioabsorbable polymer contains a monomer selected from the group consisting of a glycolide, lactide, dioxanone, caprolactone, trimethylene carbonate, ethylene glycol and lysine. By the terminology "contains a monomer" is intended a polymer which is produced from the specified monomer(s) or contains the specified monomeric unit(s). The polymer can be a homopolymer, random or block co-polymer or hetero-polymer containing any combination of these monomers. The material can be a random copolymer, block copolymer or blend of homopolymers, copolymers, and/or heteropolymers that contains these monomers.

In one embodiment, the biodegradable and/or bioabsorbable polymer contains bioabsorbable and biodegradable linear aliphatic polyesters such as polyglycolide (PGA) and its random copolymer poly(glycolide-co-lactide) (PGA-co-PLA). The FDA has approved these polymers for use in surgical applications, including medical sutures. An advantage of these synthetic absorbable materials is their degradability by simple hydrolysis of the ester backbone in aqueous environments, such as body fluids. The degradation products are ultimately metabolized to carbon dioxide and water or can be excreted via the kidney. These polymers are very different from cellulose based materials, which cannot be absorbed by the body.

These materials are also effective drug carriers for pharmaceutical products, as they meet several drug release criteria including a biocompatible and biodegradable polymer matrix that provides efficient drug loading. The degradation rate of these materials, as well as the release rate of entrapped drugs, can only be roughly controlled by varying the molecular structure and the molecular weight as there is no linear relationship between the physical properties of the constituent homopolymers or their copolymers. However, by controlling the filament diameter (to nanometer sizes) and the assembly morphology as described more fully below, the degradation rate and the drug release rate can be finely tuned. For example, Dunne et al. examined the influence of processing conditions, particle characteristics and media temperature on the degradation of PGA-co-PLA spherical particles. They found that a linear relationship between the degradation rate and particle size existed, with the larger particles degrading fastest.

Other examples of suitable biocompatible polymers are polyhydroxyalkyl methacrylates including ethylmethacrylate, and hydrogels such as polyvinylpyrrolidone, polyacrylamides, etc. Other suitable bioabsorbable materials are biopolymers which include collagen, gelatin, alginic acid, chitin, chitosan, fibrin, hyaluronic acid, dextran, polyamino acids, polylysine and copolymers of these materials. Any combination, copolymer, polymer or blend thereof of the above examples is contemplated for use according to the present invention. Such bioabsorbable materials may be prepared by known methods.

Particularly useful biodegradable and/or bioabsorbable polymers include polylactides, poly-glycolides, polycarprolactone, polydioxane and their random and block copolymers. Examples of specific polymers include poly D,L-lactide, polylactide-co-glycolide (85:15) and polylactide-co-glycolide (75:25).

Preferably, the biodegradable and/or bioabsorbable polymers used in the articles of the present invention will have a molecular weight in the range of about 1,000 to about 8,000,000 g/mole, more preferably about 4,000 to about 250,000 g/mole.

By the terminology "composite of different biodegradable and/or bioabsorbable fibers" is intended any combination of the different fibers interleaved with each other in the form of a fibrous matrix, which can be in the form of a membrane or other three dimensional form of tailored geometry, such as a tube, rod or plug.

By the terminology "asymmetric composite of different biodegradable and/or bioabsorbable fibers" is intended a composite of different biodegradable and/or bioabsorbable fibers, having at least one of non-homogeneous porosity or assembled morphology, variations in the ratio of different fibers, progressing through different regions of the composite material. For example, with reference to a membrane containing an asymmetric composite of different biodegradable and/or bioabsorbable fibers, the porosity, morphology or variations in fibers can be varied either in a direction perpendicular to or parallel with the surface of the membrane. Thus, an asymmetric composite of different biodegradable and/or bioabsorbable fibers can have 100 percent submicron diameter fibers on a first side of the membrane, zero percent submicron diameter fibers on the opposite side, and a progressively lower percentage of submicron diameter fibers in the direction from the first side across the thickness of the membrane.

By the terminology "different biodegradable and/or bioabsorbable fibers" is intended to include fibers of different diameters, fibers of different biodegradable and/or bioabsorbable materials, or fibers of both different diameters and different biodegradable and/or bioabsorbable materials.

By the terminology "fibers of different diameters" is intended that the article will include fibers having at least two different target (or intended) diameters.

By the terminology "fibers of different biodegradable and/or bioabsorbable materials" is intended to include fibers having different chemical composition, in the form of, for example, different polymeric materials, different molecular weights of the same polymeric material, or different additives (or concentration of additives), such as medicinal agents.

In one embodiment, the article will contain different fibers having diameters in the range from a few up to about 1,000 nanometers, more preferably about 10 up to about 1000 nanometers and most preferably about 20 to about 500 nanometers.

The article can contain fibers having different diameters with a controlled percentage of sub-micron diameter fibers. Preferably, the article will contain at least about 10 wt % of sub-micron diameter fibers, more preferably at least about 20 wt %, and most preferably at least about 50 wt %.

Optionally, the fibrous article can contain at least one medicinal agent. In such a case, one or more medicinal agents may be incorporated into the fibers of the article. Preferably, the medicinal agent(s) will be mixed with the bioabsorable material, e.g., polymer, prior to formation of the fibers.

In loading the medicinal agent, the medicine may need to be dissolved in a solvent that may not be compatible with the solvent used in the electrospinning process. A block copolymer, acting as a surfactant, can then be used to circumvent this difficulty. One block that forms the micellar shell is a polymer that is compatible with the fibrous material that will be used to form the nano-fibers and the other block that has a different chemical composition is more compatible with the medicinal agent. For example, a block copolymer of PLA-co-PEO could form a micelle that is compatible with the PLA solution while the inner PEO core that is more hydrophilic can be used to load more hydrophilic medicinal agents. The micellar property and uptake capacity can be determined by the chemical composition of the blocks, the molecular architecture, the block length, and the chain length ratio of the blocks. The micelles, being compatible with the fibrous material can be incorporated into the nano-fibers during processing. Furthermore, the drug release rate can also be controlled by the micellar property. For example, a glassy core can reduce the drug release rate.

By the term "medicinal agent" is intended any substance or mixture of substances which may have any clinical use in medicine. Thus medicinal agents include drugs, enzymes, proteins, peptides, glycoproteins, hormones or diagnostic agents such as releasable dyes or tracers which may have no biological activity per se, but are useful for diagnostic testing, e.g., MRI.

Examples of classes of medicinal agents that can be used in accordance with the present invention include antimicrobials, analgesics, antipyretics, anesthetics, antiepileptics, antihistamines, anti-inflammatories, cardiovascular drugs, diagnostic agents, sympathomimetic, cholinomimetic, antimuscarinics, antispasmodics, hormones, growth factors, muscle relaxants, adrenergic neuron blockers, anti-neoplastics, immunosuppressants, gastrointestinal drugs, diuretics, steroids and enzymes. It is also intended that combinations of medicinals can be used in accordance with the present invention.

Thus, in one embodiment of the present invention focal delivery and application of a medicinal agent to the wound site is achieved. Focal application can be more desirable than general systemic application in some cases, e.g., chemotherapy for localized tumors, because it produces fewer side effects in distant tissues or organs and also concentrates therapy at intended sites. Focal application of growth factors, anti-inflammatory agents, immune system suppressants and/or antimicrobials by the membranes of the present invention is an ideal drug delivery system to speed healing of a wound or incision. Focal application of anesthetics by the articles of the present invention is an ideal drug delivery system for pain management.

In one embodiment, the above described fibrous articles are in the form of a membrane. Although the discussion that follows is directed to membranes in accordance with the invention, it should be understood that the discussion is applicable to other three dimensional articles, including, but not limited to tubes, rods, plugs, blocks, etc.

In one aspect the invention is directed to biodegradable and/or bioabsorbable membranes having a controlled biodegradation rate. The chemical composition, i.e., specific polymers or blends of polymers, the fiber diameter, the membrane morphology, the molecular weight distribution and the porosity of the membrane can be used to control the degradation and/or absorption time for the membrane. As such, the membranes containing medicinal agents within the fibers themselves are well suited as a controlled drug delivery device, since the above-mentioned factors can also be used to control the rate of release of the medicinal agent.

The membrane can also contain a plurality of fibers which have different medicinal agents or different concentrations of medicinal agents. Such membranes offer unique treatment options with combinations of medicinal agents and release profiles.

In one embodiment, the membrane can contain a plurality of biodegradable and/or bioabsorable non-woven layers. The layers can have the same or different chemical composition, fiber diameters, membrane morphology and porosity as discussed more fully above. Multiple layered membranes can offer yet another way to precisely control degradation and drug release rate.

In such an embodiment, it is also contemplated that medicinal agents can be incorporated between the layers of the multi-layered membrane, instead of or in addition to, incorporating the agents into the fiber structure itself.

In one embodiment, the membrane can be attached to a non-absorbable reinforcement layer, such as a Marlox mesh.

In another aspect, the invention relates to a fibrous article formed by elecrospinning different fibers of different materials, in which the article contains a composite of different fibers containing fibers of at least one biodegradable material and fibers of at least one non-biodegradable material.

In addition to drug delivery devices, the membranes of the present invention are particularly well suited for use as an adhesion-reducing barrier.

The membranes of the present invention may be employed as barriers between tissues or barriers between tissue and bone to prevent binding of tissue to tissue or of tissue to bone. Examples of uses of the devices of the present invention include, but are not limited to, barriers between the internal female reproductive organs (e.g., uterus, fallopian tubes, ovaries); barriers between the internal female reproductive organs and the peritoneum; barriers for use during laparoscopy; barriers between periodontal tissue; barriers between cartilage or between cartilage and bone; barriers between digestive organs; spinal barriers; barriers between digestive organs and peritoneum; barriers between the epicardium and surrounding structures such as the pericardium, mediastinal fat, pleura, and sternum; barriers between tendons and tendon sheaths, such as those in the wrist and ankle; bone fracture wraps; barriers between muscle tissue and bone; barriers between the esophagus and mediasternum; barriers between the gall bladder or pancreas and the peritoneum; and barriers for scrotal surgery.

The membranes of the present invention may also be used for guided tissue regeneration. For example, the membranes may be used to cover internal perforations, such as, for

example, perforations in blood vessels, internal organs, the nasal septum, and the eardrum membrane, and may be used to reconstruct the abdominal wall, or to reinforce areas prone to or showing scar formation, such as, for example, inguinal hernias. The membrane therefore acts as a patch for covering the perforation until complete healing, followed by copolymer absorption, is achieved. It is also contemplated that the membranes may be employed as a cover for burns, whereby the device acts as a patch until the burn is healed.

The membranes of the present invention may be employed as a scaffolding to treat ulcers. A porous membrane can be designed to stimulate the proliferation of fibrous tissue, as a consequence of which, for example, in the case of ulcers, the wound bed becomes more optimal for the regeneration of skin.

The membranes of the present invention may also be employed in redirect healing, whereby the devices are employed to protect nerves and organ coverings, and mucosa during the healing process, whereby the formation of fibrous tissue over such nerves, organs, and mucosa is prevented.

The membranes may also be employed to prevent the formation of internal blood clots after surgery or traumatic injury.

The membranes may also be employed in covering denuded epithelial surfaces or weakened areas such as damaged middle ear mucosa or other mucosal surfaces, thinned vascular walls, or surgically denuded areas, such as, for example, surgically denuded areas of the pelvis.

The membranes may also be employed as anti-fibroblastic growth barriers, or as nerve coaptation wraps for connecting or repairing severed nerve ends or for repairing inflamed nerves.

The membranes of the present invention may be formed or constructed into various shapes including, but not limited to, flat sheets, tubes, rods or other three dimensional articles, as necessary to facilitate use in a particular application.

A post surgical anti-adhesion barrier or membrane of the present invention is generally used in the form of a sheet of a desired size and shape. A surgeon may cut a custom shape from preformed sheets to suit particular applications. After the membrane is shaped for a suitable fit, the flexible nature of the membrane enables the surgeon to conform the membrane to fit around the area of injury. The membrane can be formed into a strip which wraps around the organ, e.g., an intestine, to prevent formation of adhesions. An anti-adhesion membrane according to the present invention can incorporate ties or straps which connect to the membrane and which are used to tie or otherwise secure the membrane to an area of injury. It is further contemplated that the anti-adhesion membranes of the present invention may be affixed to the wound site by surgical fasteners or sutures. The flexible nature of the present anti-adhesion membrane allows the membrane to flex and bend along with normal movements of the body without being overly restrictive.

Thus, the invention is also directed to a method for reducing post-surgical adhesions. The method involves positioning an adhesion-reducing barrier between the site of surgical activity and neighboring tissues. The adhesion-reducing barrier will contain a biodegradable and/or bioabsorbable membrane. The membrane is preferably the biodegradable and/or bioabsorbable membranes discussed above. The membrane can also be a biodegradable and/or bioabsorbable membrane which contains a plurality of layers, with at least two layers having different biodegradable and/or bioabsorbable fibers from each other or contains sub-micron diameter biodegradable and/or bioabsorbable fibers, having at least one medicinal agent contained within the fibers. Preferably, the membrane will contain an antibiotic.

All embodiments of surgical adhesion barriers or membranes as described herein are well-suited for application by techniques involving endoscopy. Endoscopic surgical procedures involve the use of cannulas or tubes which provide narrow openings into a body and allow minimally invasive access to surgical targets. In laparoscopic procedures, surgery is performed in the interior of the abdomen through small tubes inserted therein. Endoscopes are frequently used as viewing devices inserted through the cannulas which allow surgeons to see the interior of the body.

Certain endoscopic and laparoscopic procedures may require that the surgical region be insufflated. Accordingly, any instrumentation inserted into the body should be substantially sealed to ensure that gases do not enter or exit the body through the incision. Moreover, endoscopic and laparoscopic procedures often require the surgeon to operate on organs, tissues and/or vessels far removed from the incisions. Thus, instruments used in such procedures are typically long and narrow while being functionally controllable from a proximal end of the instrument.

In accordance with the present invention any apparatus for deploying and positioning any of the adhesion barriers or membranes disclosed herein may be inserted through a cannula and deposited at a target site. Once the barrier is positioned as desired, it may optionally be sutured, stapled or otherwise fastened to the target site with instruments designed to be inserted through a cannula.

Thus, in another aspect, the invention is directed to a method of reducing surgical adhesions which involves positioning an adhesion-reducing barrier between the site of surgical activity and neighboring tissue. More specific applications are discussed above.

Nanofiber Fabrication Technique for Biodegradable and/or Bioabsorbable Polymers: Electrospinning Membranes with Different Biodegradable and/or Bioabsorbable Fibers

The membranes according to the present invention are preferably produced by electrospinning using a multiple jet system. Preferably, the multiple jet system includes an array of spinnerets for introducing conducting fluid containing the biodegradable and/or bioabsrobable fiberizable material. The use of a multiple jet system to produce membranes in accordance with the invention is possible by having independent control over different jets. Thus, different jets can produce different fibers as discussed more fully above.

Moreover, sub-micron diameter fibers can be produced in accordance with the invention at a relatively high yield. For example, a 40% polymer solution being spun from a single spinneret with a diameter of 700 microns, which results in a final filament having a diameter of 250 nm, will have a draw ratio of 7.84×10^6. If the extrudate (conducting fluid) from each spinneret has a rate of about 10 μl/min, the final filament speed will be about 136 m/s for each spinneret, which is a relatively high spinning rate. Thus, a commercially viable process for making membranes according to the invention is achievable with a sufficient number of spinnerets operating at such speeds.

The conducting fluid will preferably include a solution of the polymer materials described more fully above. The polymer material used to form the membrane is first dissolved in a solvent. The solvent can be any solvent which is capable of dissolving the polymer and providing a conducting fluid capable of being electrospun. The solvent is preferably selected from N,N-Dimethyl formamide (DMF), tet-

rahydrofuran (THF), N-N-dimethyl acetamide (DMAc), methylene chloride, dioxane, ethanol, chloroform or mixtures of these solvents.

The conducting fluid can optionally contain a salt which creates an excess charge effect to facilitate the electrospinning process. Examples of suitable salts include NaCl, KH_2PO_4, K_2HPO_4,KIO_3, KCl, $MgSO_4$, $MgCl_2$, $NaHCO_3$, $CaCl_2$, or mixtures of these salts.

The polymer solution forming the conducting fluid will preferably have a polymer concentration in the range of about 1 to about 80 wt %, more preferably about 10 to about 60 wt %. The conducting fluid will preferably have a viscosity in the range of about 50 to about 2000 mPa·s, more preferably about 200 to about 700 mPa·s.

The electric field created in the electrospinning process will preferably be in the range of about 5 to about 100 kilovolts (kV), more preferably about 10 to about 50 kV. The feed rate of the conducting fluid to each spinneret (or electrode) will preferably be in the range of about 0.1 to about 1000 microliters/min, more preferably about 1 to about 250 microliters/min.

A particular apparatus for producing membranes according to the present invention, which uses a multiple jet electrospinning system, is shown schematically in FIG. **1**. Equipment not essential to the understanding of the invention such as heat exchangers, pumps and compressors and the like are not shown.

Referring now to FIG. **1**, the conducting fluid, which contains the biodegradable polymer, is supplied by a micro-flow pump system **1**. The conducting fluid preferably contains a biodegradable polymer, a solvent and a salt, e.g., 25 wt % PLA-DMF solution with 1 wt % KH_2PO_4. Optionally, one or more medicinal agents can be incorporated into the conducting fluid. The pump system **1** is linked to a computer **2** which controls the flow rate of the conducting fluid to selected spinnerets by controlling pressure or flow rate. The flow rate can be changed depending upon the speed of the support membrane **3** and the desired physical characteristics of the membrane, i.e., membrane thickness, fiber diameter, pore size, membrane density, etc.

The pump system **1** feeds the conducting fluid to a multiple jet system **4** that contains manifolds **5** having a bank of spinnerets **6**. A charge in the range of about 20 to about 50 kV is typically applied to the spinnerets by a high voltage power supply **7**. A hood **8** is positioned over the multiple jet system **4** to remove the solvent at a controlled evaporation rate.

A ground plate **9** is positioned below the multiple jet system **4** such that an electric field is created between the charged spinnerets **6** and the ground plate **9**. The electric field causes tiny jets of the conducting fluid to be ejected from the spinnerets and spray towards the ground plate **9**, forming small, e.g., sub-micron, diameter filaments or fibers.

A moving support **3** is positioned between the charged spinnerets **6** and the ground plate **9** to collect the fibers which are formed from the spinnerets and to from an interconnected web of the fibers. The support **3** moves in the direction from the unwind roll **10** to the rewind roll **11**.

The micro-flow control/pumping system is electrically isolated from the ground and is powered by an isolation transformer **12**.

The post-spinning processors **13** have the functions of drying, annealing, membrane transfer (for example, from a stainless steel mesh substrate to another substrate, e.g., a Malox mesh) and post conditioning.

Multiple jets with designed array patterns can be used to ensure the fabrication of uniform thickness of the membrane. Hood, heating and sample treatment chambers can also be included to control the solvent evaporation rate and to enhance the mechanical properties. The recovered thickness can be precisely controlled from tens of microns to hundreds of microns. While additional embodiments or modifications to the electrospinning process and apparatus are described below, a more detailed description of an apparatus and method for electrospinning polymeric fibers is set forth in co-pending, commonly owned patent application, Ser. No. 09/859,004, entitled "Apparatus and Methods for Electrospinning Polymeric Fibers and Membranes," filed on even date herewith and incorporated herein for all purposes by reference.

Variation of Electric/Mechanical Properties of Conducting Fluid

The properties of the resulting membrane produced by electrospinning will be affected by the electric and mechanical properties of the conducting fluid. The conductivity of the macromolecular solution can be drastically changed by adding ionic inorganic/organic compounds. The magneto-hydrodynamic properties of the fluid depend on a combination of physical and mechanical properties, (e.g., surface tension, viscosity and viscoelastic behavior of the fluid) and electrical properties (e.g., charge density and polarizability of the fluid). For example, by adding a surfactant to the polymer solution, the fluid surface tension can be reduced, so that the electrostatic fields can influence the jet shape and the jet flow over a wider range of conditions. By coupling a pump system that can control the flow rate either at constant pressure or at constant flow rate, the effect of viscosity of the conducting fluid can be controlled.

Electrode Design

In another method for producing membranes according to the present invention, the jet formation process during electrospinning is further refined to provide better control over fiber size. Instead of merely providing a charged spinneret and a ground plate, a positively charged spinneret is still responsible for the formation of the polymer solution droplet and a plate electrode with a small exit hole in the center is responsible for the formation of the jet stream. This exit hole will provide the means to let the jet stream pass through the plate electrode. Thus, if the polymer droplet on the positively charged spinneret has a typical dimension of 2–3 mm and the plate electrode is placed at a distance of about 10 mm from the spinneret, a reasonable electrostatic potential can be developed. The short distance between the two electrodes implies that the electrostatic potential could be fairly low. However, the resultant electric field strength could be sufficiently strong for the electrospinning process. By varying the electric potential of individual spinnerets, the jet formation can be controlled and adjusted for individual spinnerets. Such an electrode configuration should greatly reduce the required applied potential on the spinnerets from typically about 15 kilovolts (kV) down to typically about 1.5 to 2 kV (relative to the ground plate potential). The exact spinneret potential required for stable jet formation will depend on the electric/mechanical properties of the specific conducting fluid.

Control of Jet Acceleration and Transportation

In another method for producing membranes according to the present invention, the jet stream flight of individual spinnerets is also precisely controlled. The jet stream passing through the plate electrode exit hole is positively charged. Although this stream has a tendency to straightening itself during flight, without external electric field confinement the jet will soon become unstable in its trajectory. In other words, the charged stream becomes defocused,

resulting in loss of control over the microscopic and macroscopic properties of the fluid. This instability can be removed by using a carefully designed probe electrode immediately after the plate electrode and a series of (equally) spaced plate electrodes. The electrode assembly (i.e., the probe electrode and the plate electrodes) can create a uniform distribution of electrostatic potential along the (straight) flight path. The acceleration potential is formed by placing the base potential of the spinneret at about +20 to +30 kV above the target (at ground potential) while the electrostatic potential of the probe electrode can be adjusted to slightly below the plate electrode base potential. The composite electrodes are capable of delivering the jet stream to a desired target area.

Jet Manipulation

In yet another method for producing membranes according to the present invention, individual jet streams can be focused by using an "Alternating Gradient" (AG) technique. The basic idea is to use two pairs of electrostatic quadrupole lenses. The second lens has the same geometric arrangement as the first lens with a reversed (alternate) electric gradient. The positively charged jet stream will be focused, for example, in the xz plane after the first lens and then be refocused in the xz plane after the second lens. It is noted that the z-direction represents the direction of the initial flight path. By applying an additional triangle-shaped waveform to the potential on one of the pairs of the quadrupole, the jet can be swept across the target area, allowing the control of the direction of the jet stream. Furthermore, with varying waveform of the 'sweep' potential, a desired pattern on the target can be formed.

Pattern Design by Electrospinning.

In yet another method for producing membranes according to the present invention, reference will be made to FIG. **2**. In this method, the conducting fluid is introduced into the electrospinning process through an array of electrospinning spinnerets **20**. The array of electrospinning spinnerets are assembled in a matrix **21** that provides electrical isolation for the spinnerets, with each spinneret having two pairs (X and Y direction) of miniature scanning electrodes **22**. The spinneret **20** and the scanning electrodes **22** are electrically wired such that each individual polymer solution jet can be turned on and off and be steered to a finite size target area. As each spinneret **20** can be turned on/off independently by electricity, the response time will be relatively fast. Also, each spinneret **20** can deliver a different solution, e.g., each containing a different polymer or different drug or concentration of drug. A designed pattern can be obtained in the resultant membrane. This pattern can be precisely controlled by a computer and can be tailored for specific medical applications.

Multiple Jet Slit-Die Geometry

In another apparatus for producing membranes in accordance with the present invention, reference is made to FIGS. **3**(*a*)–**3**(*c*). In this apparatus, a multiple jet system **30** comprises an array of electrospinning spinnerets **31**, each spinneret **31** being defined by a slit **32** formed in a slit-die **33** that is coupled to high voltage to serve as an electrode disposed above the ground plate **34**. As shown in detail in FIG. **3**(*c*), the spinnerets **31** are each interconnected by selectively narrow slits **35**, such that each spinneret **31** is interconnected to a neighboring spinneret **31** by a slit **35**. The conducting fluid will not flow through the slits **35**, but will flow through each of the spinnerets **31** in a more robust manner.

The slit-die approach permits three distinct advantages that are not available by using individual spinnerets. (1) The slit-die is made up of two separate components with controlled dimensions of the effective openings for the spinnerets. In other words, by changing the distance between the two components, the effective openings of the spinnerets become available. (2) The presence of slits between the larger openings permits fluid flow and thereby equalizes the pressure difference between the spinnerets. (3) The presence of slits can also reduce potential blockage of the fluid.

The membranes produced by the slit-die approach can achieve a larger degree of flexibility in the structures. For example, different size nanofibers can be produced from the same slit-die setup.

Control of Degradation Rate through Processing Parameters

As discussed above, very different fiber diameter and morphology in the membrane can be obtained by changing the parameters in the electrospinning process. As the degradation rate is inversely proportional to the fiber diameter, the manipulation capability through processing parameters provides not only the means to control the degradation rate of the membrane but also the ways to control drug loading efficiency and the drug release rate.

For example, it is believed that a change in charge density (through the addition of salts) can significantly affect the fiber diameter. When 1 wt % potassium phosphate (KH_2PO_4) was added to a PLA-co-PGA solution, the fiber diameter became much thinner (see SEM picture in FIG. **4**) than the one with no salt added (FIG. **5**). Thus, it is believed that higher excess charge density generally favors the production of thinner fibers and lower excess charge density favors the production of thicker fibers. Several other kinds of salts (e.g. NaCl, KH_2PO_4, KIO and K_3PO_4), which are all biologically compatible to the body, are also contemplated.

Control of Drug Release Rate and Test of Antibacterial Effect

It is also believed that when a drug is incorporated into the fibers of the membrane, the drug release rate is a function of fiber diameter. As such, the release rate of a drug trapped in the membrane can be precisely controlled. Many surgical procedures often lead to adhesion formation involving the colon and rectum. This additionally increases the risk of post-operative infection. The addition of antibiotics to the membrane with scheduled release may be used to reduce the risk of abscess and infection.

EXAMPLES

The following non-limiting examples have been carried out to illustrate preferred embodiments of the invention. These examples include the preparation of membranes according to the invention, analysis of the membranes and testing of the membranes.

Example 1

A membrane was prepared as follows: a 30 wt % PLG copolymer/DMF solution was prepared by slowly dissolving PLG copolymer pellets (inherent viscosity of 0.55–0.75. Birmingham Polymers Inc., AL) into an N,N-dimethyl formamide (DMF) solvent at room temperature. The solution was then loaded into the 5 ml syringe fitted with a gauge 20 needle, and delivered through a Teflon tube (0.03" ID) to the exit hole of an electrode having a diameter of 0.025". The solution was pumped and controlled by a syringe pump (Harvard Apparatus "44" series, MA) at a flow rate of 20 microliters/min. A 25 kV positive high voltage (by Glassman High Voltage Inc.) was applied on the electrode. The distance from the tip of the electrode to the grounded collecting plate was 15 cm. A tiny electrospinning jet was formed and stabilized in 30 seconds under these conditions. The col-

lecting plate was movable and controlled by a stepper motor. The collecting plate was continually moved at a rate of 1 mm/sec until a membrane having a relatively uniform thickness of about 100 microns was obtained. An SEM (Scanning Electron Microscopy) image of the membrane is shown in FIG. **6**.

Example 2

A biodegradable and bioabsorbable membrane according to the present invention, fabricated by a multi-jet electrospinning process, was prepared as follows: an 8 wt % polyacrylonitrile (Aldrich Chemical Company, Inc.)/DMF solution was prepared by slowly adding and dissolving the polymer powders into an organic solvent, which was DMF (N,N-dimethyl formamide), at room temperature. After the solution was completely mixed, it was then loaded into 6 individual syringes, each with a volume of 5 mL. The syringes were fitted with gauge 20 needles and the solution was delivered through Teflon tubes (0.03" ID) to 6 electrodes, each having a tiny hole with a diameter of 0.025". The polymer solution was finally pumped and controlled by a syringe pump (Harvard Apparatus "44" series, MA) at a flow rate of 25 microliters/min. In addition, a 26 kV positive high voltage (by Glassman High Voltage Inc.) was applied on the electrodes in order to obtain the existence of six well-stabilized electrospinning jets. The distance from the tip of the electrodes to the grounded collecting plate was 15 cm and the tips of the electrodes were spaced about 2 cm apart from each other. Closer spacing between electrodes (spinnerets) could have been achieved by changing appropriate parameters, e.g., by increasing the applied electric potential. The collecting plate was movable and controlled by a step motor. The collecting plate was continually moved at a rate of 1 mm/sec until a bioabsorable and biodegradable membrane having a relatively uniform thickness of about 100 microns was obtained.

Example 3

A polymer solution suitable for electrospinning, which contained a drug, was prepared as follows: A sample of Poly(DL-lactide) ("PLA") purchased from Birmingham Polymers, Inc., Birmingham, Ala. (Product No. D98120) having a weight average molecular weight of 1.09×10^5 g/mole and a polydispersity of 1.42 was stored in a vacuum oven at room temperature. The pellets were dissolved in DMF purchased from Fisher Scientific, Fair lawn, N.J. to form a 25 wt % solution. The antibiotic drug used was Mefoxin™ from Merck & Co., Inc., West Point, Pa. The antibiotic was dissolved in distilled water and then mixed with PLA/DMF solution in appropriate amounts to form the solution with a PLA/drug ratio of 9:1. A stable jet was formed using this solution in the electrospinning process described in Example 1.

Example 4

A second membrane was prepared in a similar manner to Example 1, except that a drug solution was added to the polymer solution prior to electrospinning and the voltage applied to the electrode was adjusted. The drug solution was prepared by dissolving 0.6 grams of Mefoxin (Merck & Co Inc.) into 0.4 grams of water. The drug solution was then very slowly (dropwise) added to the polymer solution with gentle stirring until it reached a final PLG/drug ratio of 19:1. A 20 kV positive high voltage (by Glassman High Voltage Inc.) was applied on the electrode. All other parameters were the same as Example 1. An SEM (Scanning Electron Microscopy) image of the membrane containing the drug is shown in FIG. **7**.

The drug release rate was determined by placing the membrane in a phosphate buffer solution (PBS) and then by monitoring the drug concentration in the buffer solution vs. time using an ultra violet (UV) light (234 mm) absorption measurement. The drug release (in PBS buffer) profile is shown in FIG. **8**.

Example 5

A membrane was fabricated as follows: A 35 wt % PLA polymer/DMF solution was prepared by slowly dissolving the PLA pellets. The solution was fed through the syringe pump system to the electrodes at a flow rate of 20 microliters/min per jet. A 25 kV positive high voltage was applied to the electrode. FIG. **9** shows a typical scanning electron microscopy (SEM) image of an electrospun PLA membrane made by the procedures described above. It has an average fiber diameter of 200 nm. The typical membrane density is about 0.25 g/cm^3, as compared to the neat resin (PLA) density of 1.3 g/cm^3.

Example 6

An in-vitro biodegradation test was conducted to evaluate the performance of electrospun membranes. The biodegradation test was conducted using the following method, which is routinely used in the suture industry: a PGA membrane was submerged in a buffer solution containing sodium phosphate, potassium phosphate, and distilled water (pH 7.3), and maintained at 37° C. The weight loss was measured as a function of time. The test was repeated for a PLA membrane. The results for both membranes are plotted in FIG. **10**. A review of FIG. **10** reveals that the major weight loss (50%) varies from 2 weeks (PGA) to about 6 months (PLA).

Example 7

A membrane containing dual thickness fibers was prepared as follows: a 25 wt % PLA-DMF solution was prepared by slowly dissolving PLA polymer pellets having the same molecular weight and poly dispersity as in Example 3 into a DMF solvent. A drug solution was prepared by dissolving 0.6 grams of Mefoxin (Merck & Co Inc.) into 0.4 grams of water. The drug solution was then very slowly (dropwise) added to the polymer solution with gentle stirring until it reached a final PLA/drug ratio of 19:1. A 20 kV positive high voltage (by Glassman High Voltage Inc.) was applied on the electrode. All other parameters were the same as Example 1. A membrane having a network structure consisting of large size filaments (2 micron diameter), very fine fibrils (50 nanometer diameter) and small blobs was obtained by varying the solution feed rate over a range from 20 μl/min to 70 μl/min. An SEM of the resulting membrane is shown in FIG. **11**.

The membrane was then placed in the buffer solution described in Example 6. After one week of degradation in the control buffer, the fine fibers completely disappeared (FIG. **12**). A comparison of FIGS. **11** and **12** reveals that this morphology results in a rapid weight loss in the first week. Thus, if more rapid weight loss is desired, a membrane having a higher concentration of thin fibrils can be produced.

Example 8

An experiment was conducted to evaluate the barrier properties of different membranes for preventing post-

operative induced adhesions. The experiment used an objective rat model (ORM) to evaluate the performance of electrospun PLA-co-PGA membranes, with and without an antibiotic drug (Mefoxin) contained in the membrane structure, which were prepared in the same manner as in Examples 1 (without the drug) and 4 (with the drug). A control group was also used for comparison.

The test procedures used were as follows: the membrane being tested was first sterilized using ^{60}Co radiation source. The membrane sample was sealed in a plastic bag in a container filled with dried nitrogen gas. The package then received γ-radiation doses from 5.15~25 kGy, depending on the mass. This procedure has been well documented in the literature.

300–450 gram male Sprague-Dawley rats were used in the experiments. They were individually housed and given food and water ad libitum both pre- and postoperatively. Anesthesia was produced using an IM ketamine (80 mg/kg) and xylaxine (10 mg/kg) injection into the right hindleg prior to the celiotomy. Euthanasia was performed using intracardiac injection of pentobarbital (60 mg/kg).

The rats were divided into two procedure groups. The first group underwent a midline celiotomy and the cecum identified and scored using an abrasive pad until serosal bleeding was noted on the anterior surface. A 1×1 cm square of abdominal wall muscle was then excised directly over the cecal wound. The first group experiment was conducted using 12 animals with the membrane and 14 animals with the membrane containing antibiotics, which were compared to 12 control animals (cecal abrasions and buttons without any membrane). The celiotomy was then closed in two layers immediately (control, n=12), after a barrier was laid in between the cecum and the abdominal wall (n=12), or after an antibiotic-impregnated barrier was placed in the aforementioned are (n=14). All rats underwent a second celiotomy after 4 weeks. The presence or absence of adhesions from the cecum to the abdominal wall was noted. The cecum was then isolated from the rest of the bowel and the breaking strength of the adhesion was measured by using a tensiometer.

In the first group of experiments, cecal adhesions were noted in 67% of the control set, 50% of the set with barriers, and 38% of the set with barriers impregnated with antibodies (see FIG. **13**). Tensiometer readings on those adhesions present were found to be 6.18, 5.76, and 4.30 respectively (see FIG. **14**). Only adhesions from the cecum to the abdominal wall were counted. Adhesional bands between the bowel and other abdominal organs were noted on occasion, but were not taken into account.

In the second group experiment, Marlex mesh, a material often used in abdominal surgery to repair the abdominal wall, was used to test the membranes. This mesh has the severe complication of causing adhesions to the intestines which not only leads to bowel obstruction, but also fistula formation. Both complications can be devastating to patients. The Marlex mesh was applied to a defect created in the abdominal wall and 10 animals had the barrier membrane interposed between the mesh and the intestines, while 10 controls had the Marlex placed with no interposing membrane. The second group of rats had Marlex mesh placed into the abdominal cavity. The abdomen was opened using a midline celiotomy and a 1×1 cm square of Marlex mesh was placed over the cecum and fixed to the abdominal wall using two silk sutures. The abdomens were then either immediately closed in two layers (control, n=10) or had a barrier placed in between the cecum and the mesh (n=10). All animals underwent a second celiotomy after 4 weeks. The presence or absence of adhesions between the cecum and mesh were noted.

In the group of rats with Marlex mesh, the first set of rats all has adhesions from the cecum to the mesh (100%). The mesh also has a multitude of other adhesions to the omentum, stomach, and liver making a measurement of adhesional strength from cecum to abdominal wall problematic. The set with barriers was found to have only one rat with adhesions from the cecum to the abdominal wall (10%).

Overall, the test results showed good barrier properties of the membranes, i.e., a low incidence of induced adhesion in the membrane embedded area, while an adhesion was induced in the control area. The membrane containing the antibiotic showed better barrier properties than the membrane without the antibiotic.

Example 9

The antibacterial effect of drug containing membranes was tested using the following procedures: 8 ml of Luria Broth (LB) and 80 microliters of *E. coli* cells were added to each of four sample test tubes. A 7.0×7.0 cm sample of a PLA electrospun membrane having a thickness of about 75 microns (with a corresponding total weight of 100 mg) was added to one of the test tubes. A second sample of a PLA membrane containing approximately 4.83 mg of Mefoxin was added to another test tube. A third sample of a PLA membrane containing approximately 8.85 mg of Mefoxin was added to a third test tube. The last test tube was used as a control.

LB was used to grow the *E. coli* bacterial cells. The sample tubes were placed in an incubator overnight. The temperature of the incubator was set at 37° C. and the shaking rate was set at 225 rpm. Shaking was necessary in order for the *E. coli* bacteria to receive enough nutrients needed to grow. Using a SmartSpec *3000 instrument, the optical density (OD) at the 600 nm wavelength for *E. coli* bacteria was recorded and the amount of cells in each test tube was calculated. The cell concentration could be related to the product of the optical density of each sample and a conversion factor. As the optical density increases (the broth becomes more turbid), the cell concentration should increase. The results are shown in FIG. **15**, with the y-axis unit being cell/ml or the bacteria concentration.

A review of FIG. **15** reveals that the growth of *E. coli* bacteria is completely prohibited by the release of the Mefoxin antibiotic drug from the membrane containing 8.85 mg of the drug. Also, it appears that the higher the loading concentration of Mefoxin, the more effective the membrane becomes.

Example 10

An in-vivo biodegradation test was conduced using a PLA electrospun membrane having an average fiber diameter in the range of about 100–150 nanometers. The membrane was fabricated as follows. A 25 wt % PLA solution in DMF was prepared. A 60 wt % Mefoxin drug in aqueous solution was then added to the polymer solution to reach a final PLA/drug ration of 9:1. A 20 kV positive voltage was applied to the electrode. An SEM of the initial as spun membrane (FIG. **16**) shows smooth fibrous structures with an average fiber diameter between 100–150 nm. The membrane was implanted into a rat and removed after one week, following the procedures described in Example 8. An SEM of the partially biodegraded membrane is shown in FIG. **17**.

A comparison of FIGS. **16** and **17** reveals that the morphology of the membrane has been changed, resulting in a more porous structure.

Example 11

A bioabsorbable composite membrane consisting of two polymer components of different hydrophobicity according to the present invention was prepared as follows: First, a 6 wt % polyethylene oxide (PEO)/DMF solution was prepared by slowly adding the polymer powders into an organic solvent, which was DMF (N,N-dimethyl formamide). Second, a 30 wt % polylactide glycolide (PLG)/DMF solution was made by dissolving the polymers into DMF as well. After these two solutions were each completely homogenized at the room temperature, they were then loaded separately into two individual syringes, each with a volume of 5 mL. Next, the syringes were fitted with 2 gauge 20 needles and delivered through Teflon tubes to the electrodes, each having a tiny hole with a diameter of 0.025". The polymer solutions were finally pumped and controlled by a syringe pump at a flow rate of 20 microliters/min. In addition, a 25 kV positive high voltage was applied on two separate electrodes in order to obtain the existence of well-stabilized electrospinning jets. The distance from the tips of the electrodes to the ground collecting plate was 15 cm. Furthermore, a step motor was utilized in order to control the movement of the ground collector so that it was capable to move in different directions, either left or right. The collecting plate was moving at a rate of 5 steps/sec continuously until a bioabsorable membrane having a relatively uniform thickness of 100 microns was achieved.

Example 12

A bioabsorbable composite membrane consisting of two component polymer blend of different hydrophobicity according to the present invention was prepared as follows: First, a 2 wt % polyethylene oxide (PEO, Mw=100,000 g/mol)/DMF solution was prepared by slowly adding the polymer powders into an organic solvent, which was DMF (N,N-dimethyl formamide). Second, a 20 wt % polylactide glycolide (PLG)/DMF solution was made by dissolving the polymers into DMF as well. These two solutions were mixed together and were each completely homogenized at the room temperature. They were then loaded separately into two individual syringes, each with a volume of 5 mL. Next, the syringes were fitted with 2 gauge 20 needles and delivered through Teflon tubes to the electrodes, each having a tiny hole with a diameter of 0.025". The polymer solutions were finally pumped and controlled by a syringe pump at a flow rate of 20 microliters/min. In addition, a 25 Kv positive high voltage was applied on two separate electrodes in order to obtain the existence of well-stabilized electrospinning jets. The distance from the tips of the electrodes to the ground collecting plate was 15 cm. Furthermore, a step motor was utilized in order to control the movement of the ground collector so that it was capable to move in different directions, either left or right. The collecting plate was moving at a rate of 5 steps/sec continuously until a bioabsorable membrane having a relatively uniform thickness of 100 microns was achieved.

Thus, while there has been disclosed what is presently believed to be preferred embodiments of the invention, those skilled in the art will appreciate that other and further changes and modifications can be made without departing from the scope or spirit of the invention, and it is intended that all such other changes and modifications are included in and are within the scope of the invention as described in the appended claims.

We claim:

1. An adhesion-reducing barrier comprising a biodegradable and/or bioabsorbable membrane, said membrane comprising a composite of different biodegradable and/or bioabsorbable fibers or an asymmetric composite of different biodegradable and/or bioabsorbable fibers.

2. An adhesion-reducing barrier according to claim 1, wherein different fibers refers to fibers of different diameters.

3. An adhesion-reducing barrier according to claim 2, wherein said fibers of different diameters include fibers having diameters less than 300 nanometers and fibers having diameters greater than 300 nanometers.

4. An adhesion-reducing barrier according to claim 2, wherein said membrane comprises at least about 20 weight percent of submicron diameter fibers.

5. An adhesion-reducing barrier according to claim 4, wherein said membrane comprises at least about 50 weight percent of submicron diameter fibers.

6. An adhesion-reducing barrier according to claim 1, wherein different fibers refers to fibers of different biodegradable and/or bioabsorbable materials.

7. An adhesion-reducing barrier according to claim 1, wherein different fibers refers to fibers of different diameters and different biodegradable and/or bioabsorbable materials.

8. An adhesion-reducing barrier according to claim 1, wherein said biodegradable and/or bioabsorbable fiberizable material comprises a biodegradable and/or bioabsorbable polymer.

9. An adhesion-reducing barrier according to claim 8, wherein said biodegradable and/or bioabsorbable polymer comprises a monomer selected from the group consisting of a glycolide, lactide, dioxanone, caprolactone, trimethylene carbonate, ethylene glycol and lysine.

10. An adhesion-reducing barrier according to claim 8, wherein said biodegradable and/or bioabsorbable polymer comprises a biodegradable and/or bioabsorbable linear aliphatic polyester.

11. An adhesion-reducing barrier according to claim 10, wherein said biodegradable and/or bioabsorbable linear aliphatic polyester is a polyglycolide or a copolymer poly (glycolide-co-lactide).

12. An adhesion-reducing barrier according to claim 1, wherein said biodegradable and/or bioabsorbable fiberizable material comprises a material derived from biological tissue.

13. An adhesion-reducing barrier according to claim 1, wherein said fibers have diameters in the range from about 10 up to 1,000 nanometers.

14. An adhesion-reducing barrier according to claim 13, wherein said fibers have diameters in the range from about 20 to about 500 nanometers.

15. An adhesion-reducing barrier according to claim 1, further comprising small blobs of biodegradable and/or bioabsorbable material.

16. An adhesion-reducing barrier according to claim 1, further comprising at least one medicinal agent.

17. An adhesion-reducing barrier according to claim 16, wherein said medicinal agent is contained within said fibers.

18. An adhesion-reducing barrier according to claim 17, further comprising fibers with different concentrations of said medicinal agent.

19. An adhesion-reducing barrier according to claim 17, further comprising fibers with different medicinal agents.

20. An adhesion-reducing barrier according to claim 1, further comprising a plurality of layers, wherein at least one of the layers comprises a composite or asymmetric composite of different biodegradable and/or bioabsorbable fibers.

21. An adhesion-reducing barrier according to claim 20, further comprising at least one medicinal agent between at least two of said layers.

22. An adhesion-reducing barrier according to claim 1, wherein said membrane has a controlled degradation rate.

23. An adhesion-reducing barrier according to claim 1, wherein said membrane has a thickness in the range of about 10 to about 5000 microns.

24. An adhesion-reducing barrier according to claim 23, wherein said membrane has a thickness in the range of about 20 to about 1000 microns.

* * * * *

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(12) **United States Patent**
Chu et al.

(10) **Patent No.: US 6,689,374 B2**
(45) **Date of Patent: Feb. 10, 2004**

(54) **BIODEGRADABLE AND/OR BIOABSORBABLE FIBROUS ARTICLES AND METHODS FOR USING THE ARTICLES FOR MEDICAL APPLICATIONS**

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(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

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(22) Filed: **Feb. 27, 2003**

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(51) **Int. Cl.**[7] **A61F 2/02**

(52) **U.S. Cl.** **424/423**; 424/424; 424/425; 424/426

(58) **Field of Search** 424/423, 424, 424/425, 426

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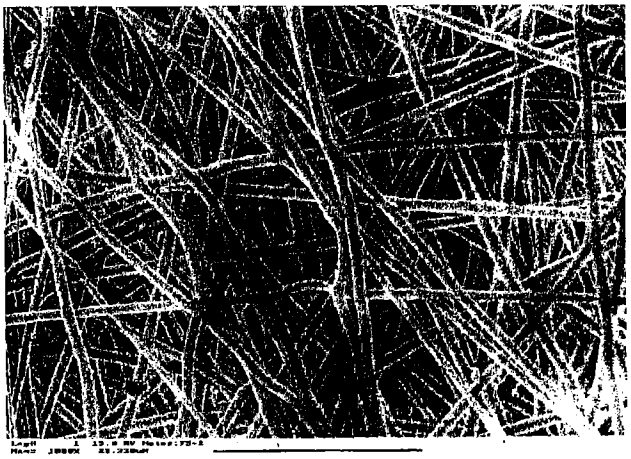
(57) **ABSTRACT**

Biodegradable and/or bioabsorable fibrous articles and methods for using the articles in medical applications are disclosed. The biodegradable and/or bioabsorable fibrous articles, which are formed by elctrospinning fibers of biodegradable and/or bioabsorbable fiberizable material, comprise a composite (or asymmetric composite) of different biodegradable and/or bioabsorbable fibers. Articles having specific medical uses include an adhesion-reducing barrier and a controlled delivery system. The methods include methods for reducing surgical adhesions, controlled delivery of a medicinal agent and providing controlled tissue healing.

29 Claims, 13 Drawing Sheets



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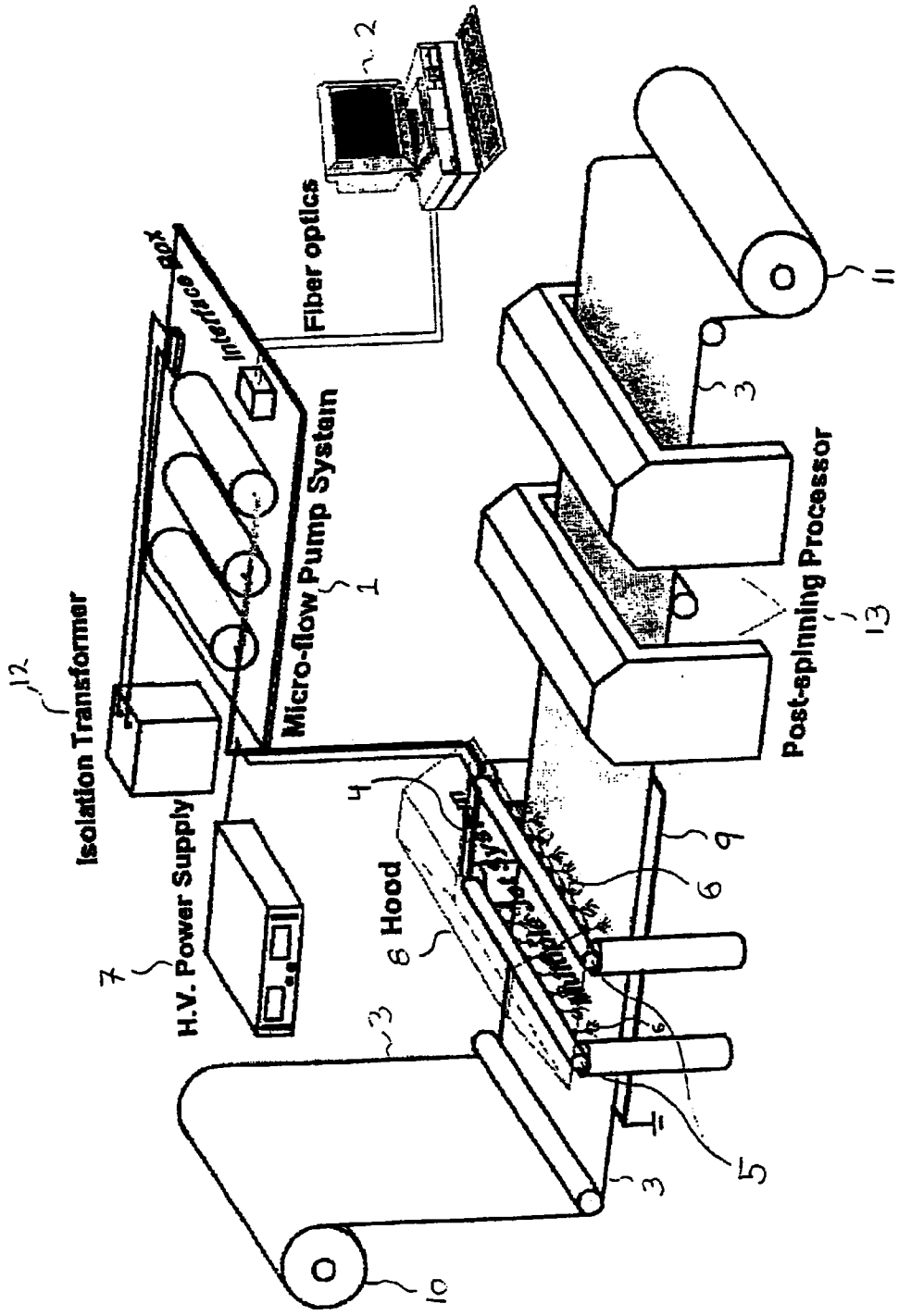

Fiber optics
Interface port
Micro-flow Pump System
Isolation Transformer
H.V. Power Supply
Hood
Post-spinning Processor

FIG-1

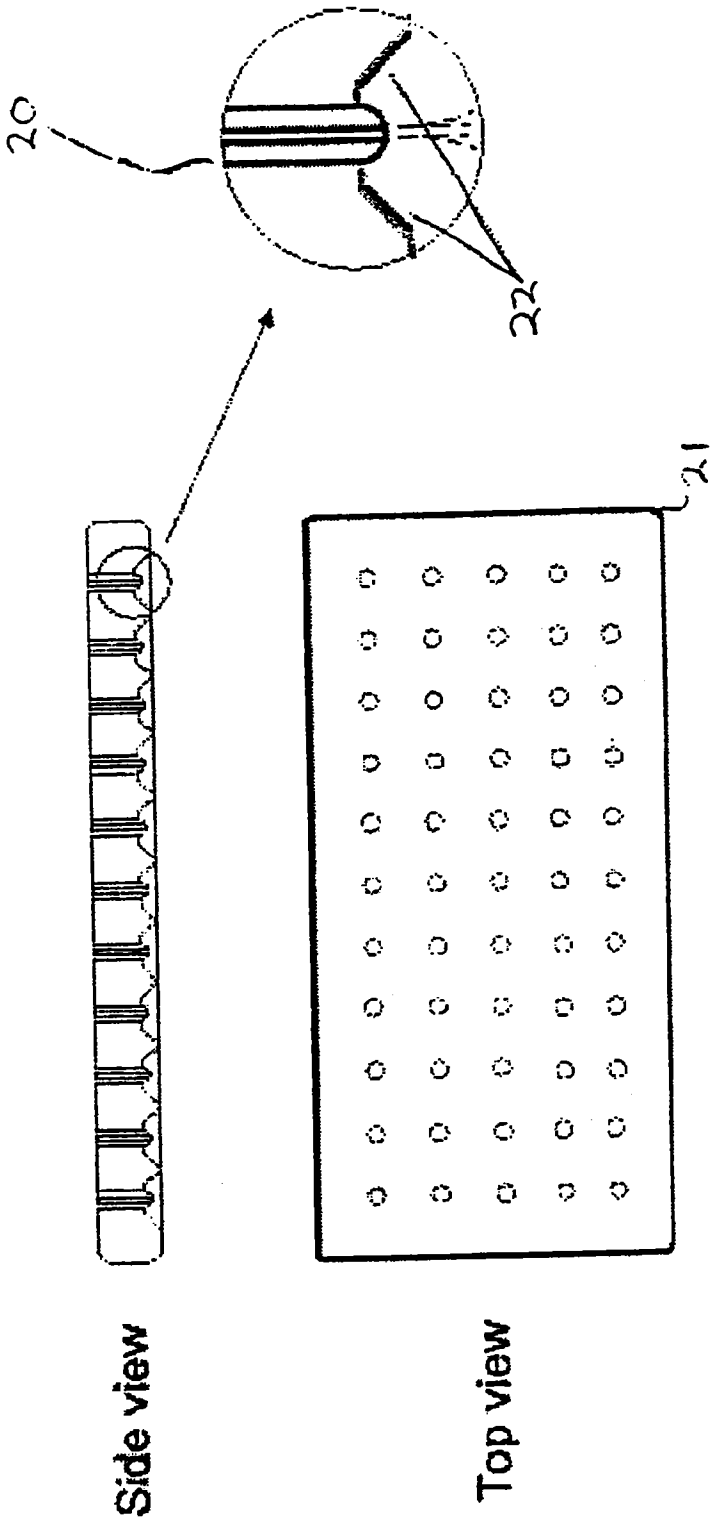


FIG-2

FIG-3 (a)

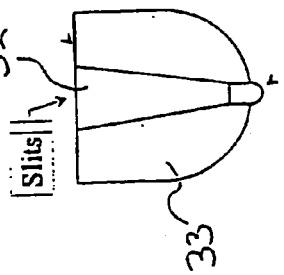


FIG-3 (b)

FIG-3 (c)

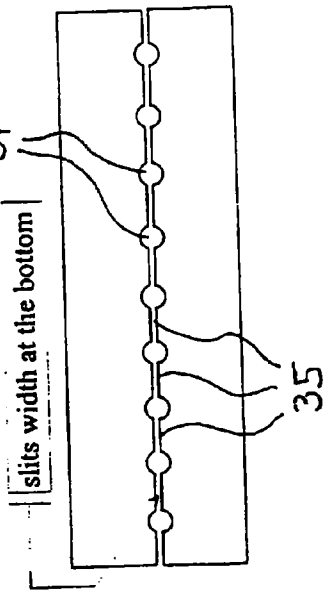


FIG-5

Spun membrane without salt

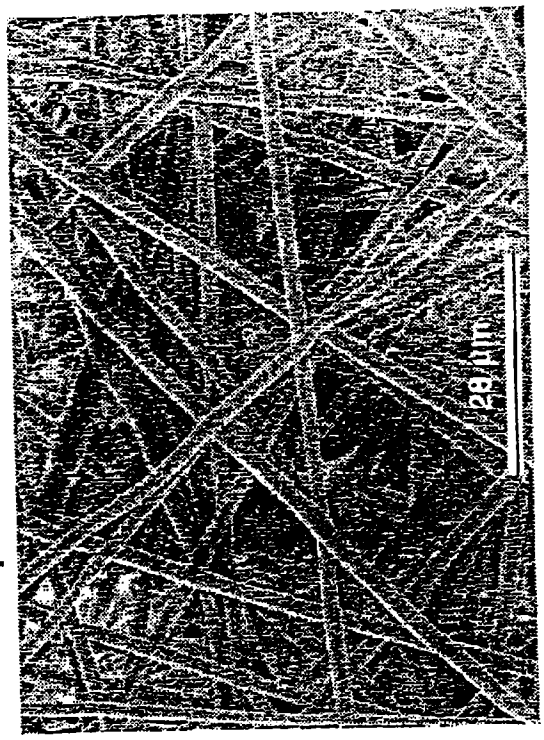
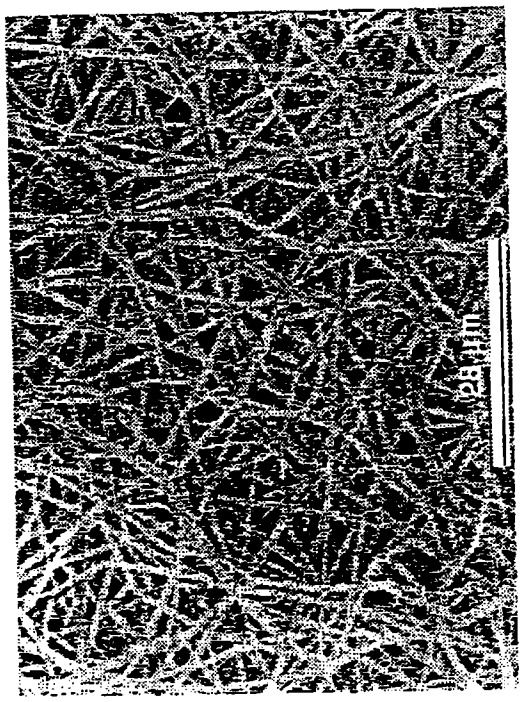


FIG-4

Spun membrane with 1 wt% KH_2PO_4



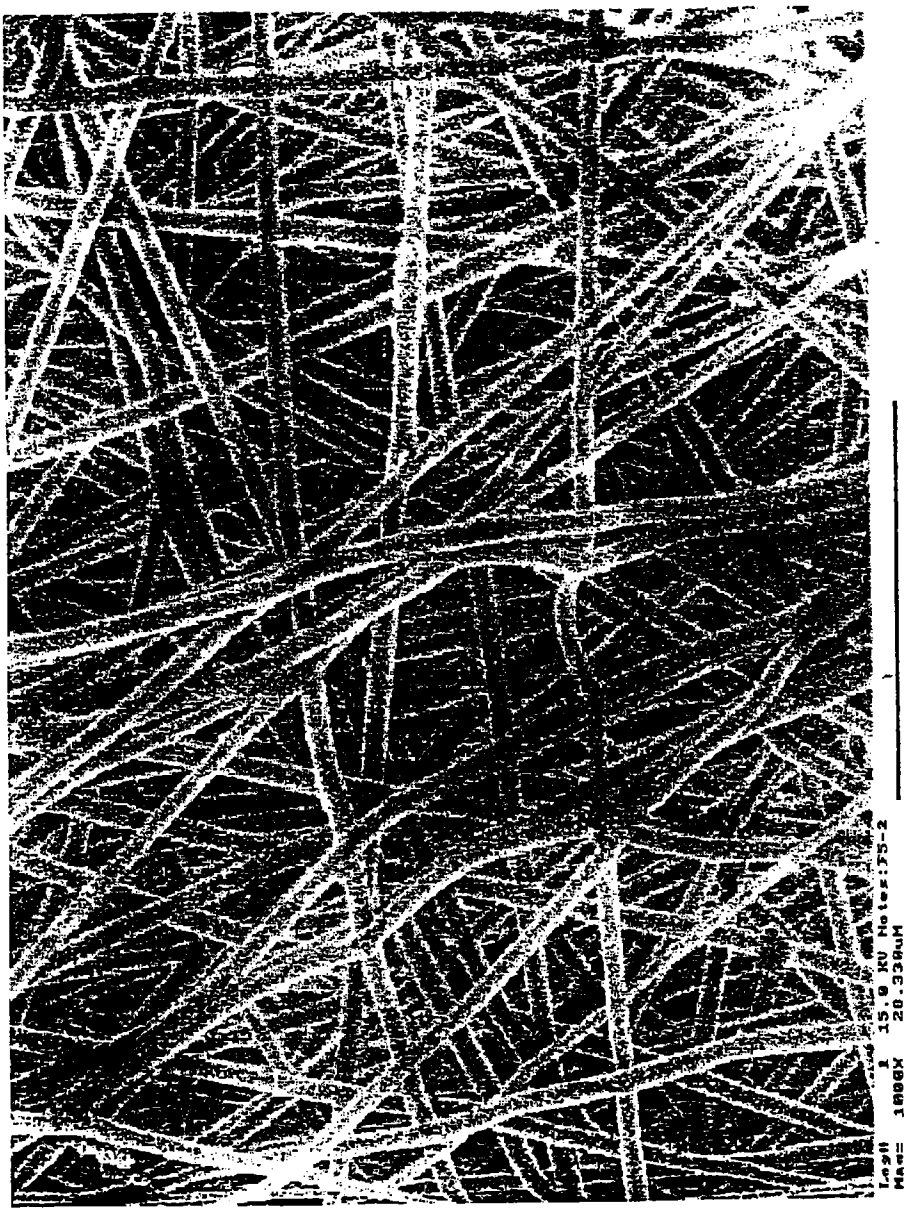


FIG-6

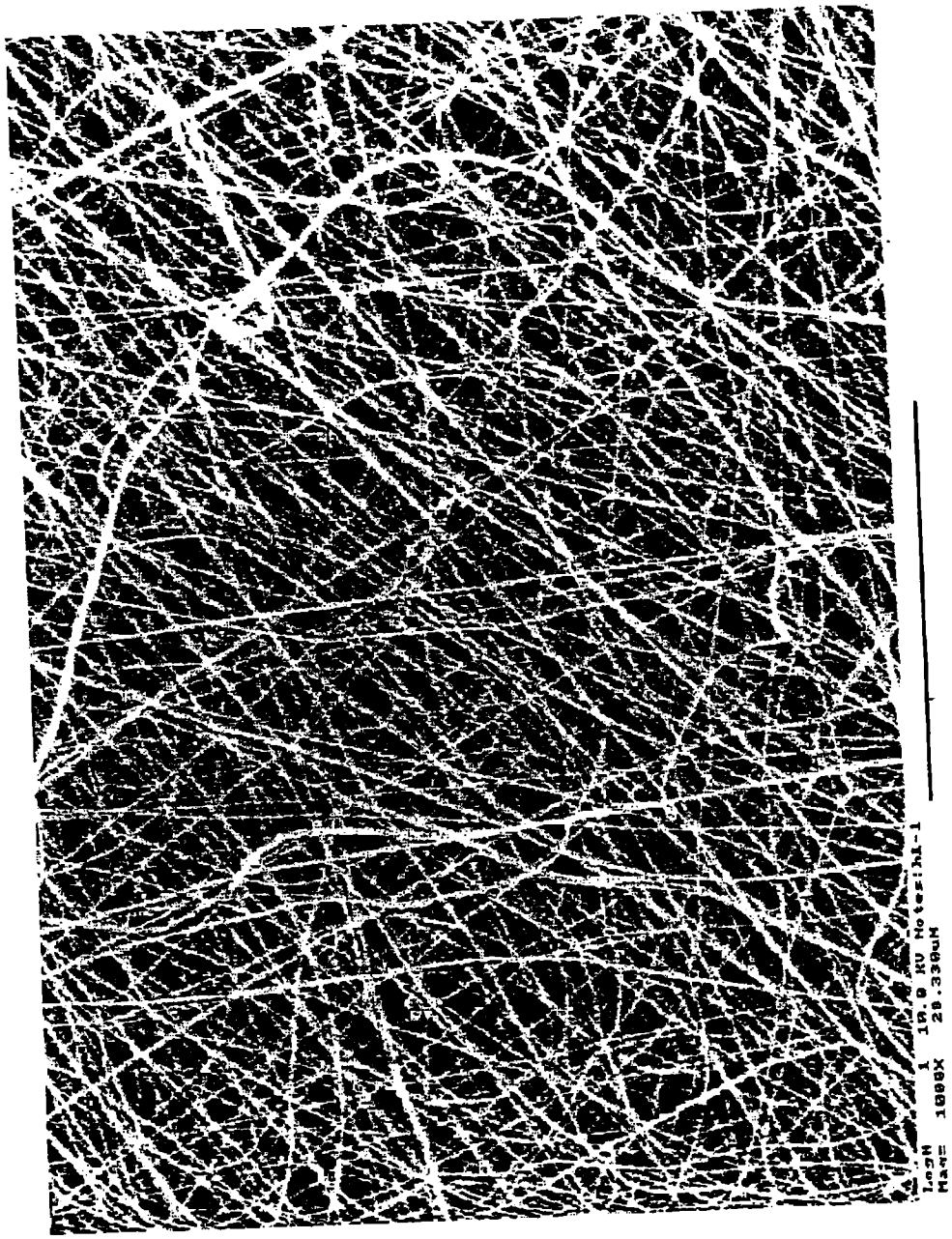


FIG-7

FIG-8

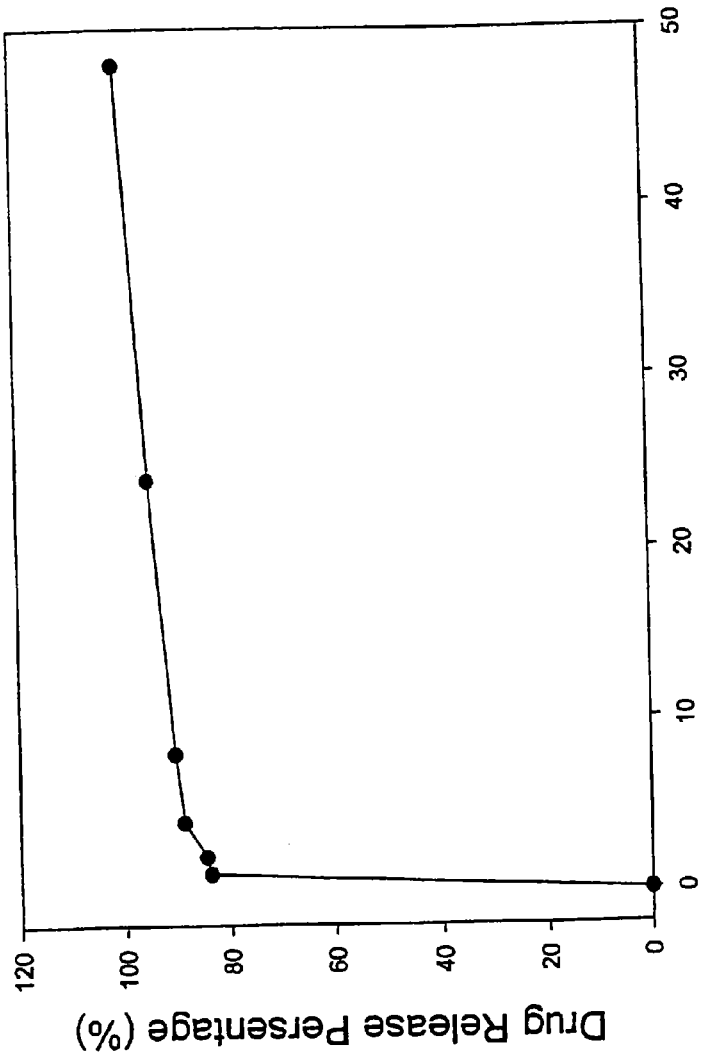

In Vitro Drug Release Profile
Drug Release Persentage (%)
0
20
40
60
80
100
120
Time (hr)
0
10
20
30
40
50

FIG-10

Biodegradation rate of electrospun membr

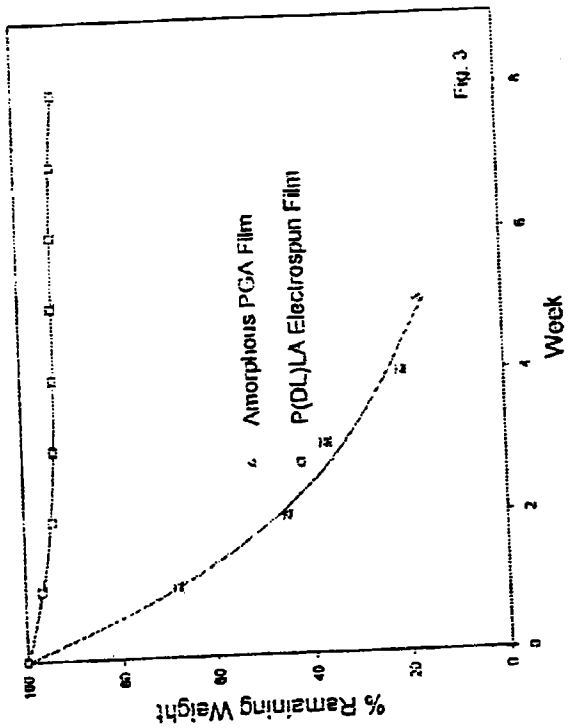


FIG-9

SEM image of electrospun PLAmembrane

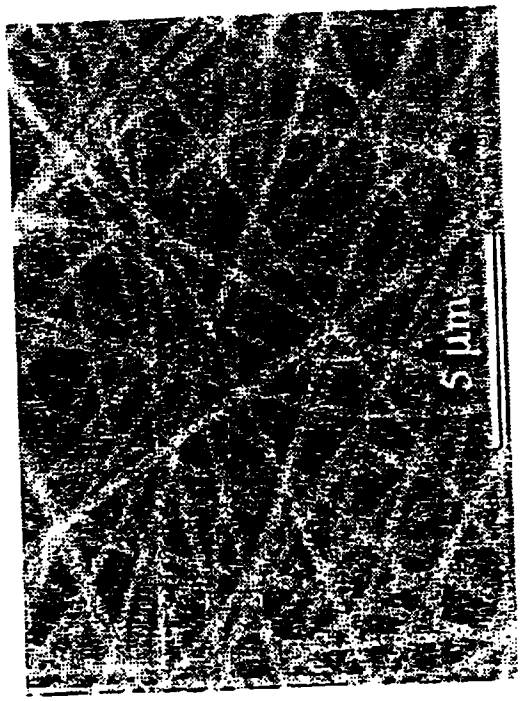


FIG-12


Membrane after 1 week of degradation

FIG-11


Duel thickness PLA membrane
1μm

FIG-13

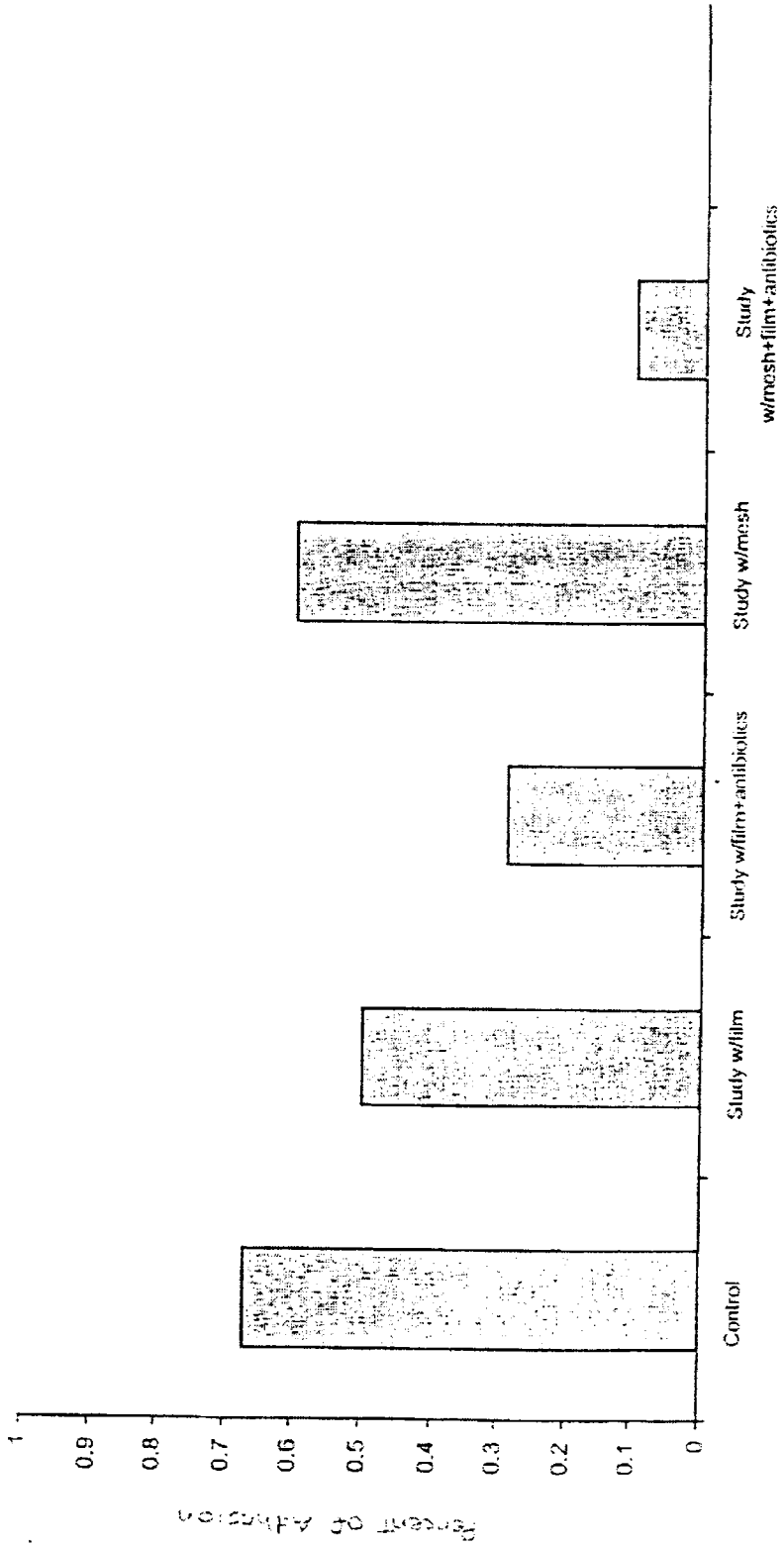

Incidence of Adhesion
Percent of Adhesion
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
Control
Study w/film
Study w/film+antibiotics
Study w/mesh
Study w/mesh+film+antibiotics

FIG-14

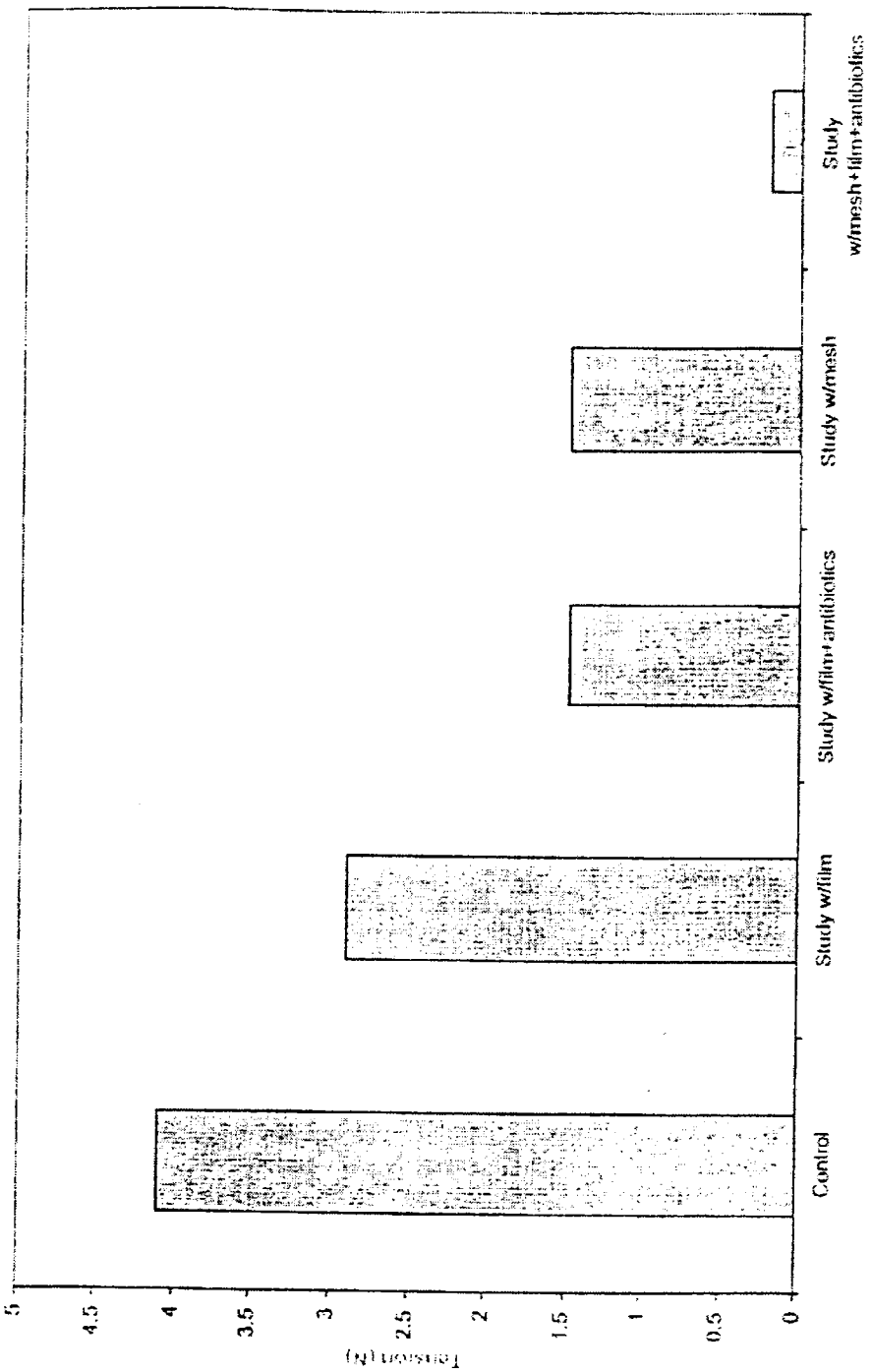

Cecal Adhesion Tension (N)
Tension (N)
5
4.5
4
3.5
3
2.5
2
1.5
1
0.5
0
Control
Study w/film
Study w/film+antibiotics
Study w/mesh
Study w/mesh+film+antibiotics

FIG-15

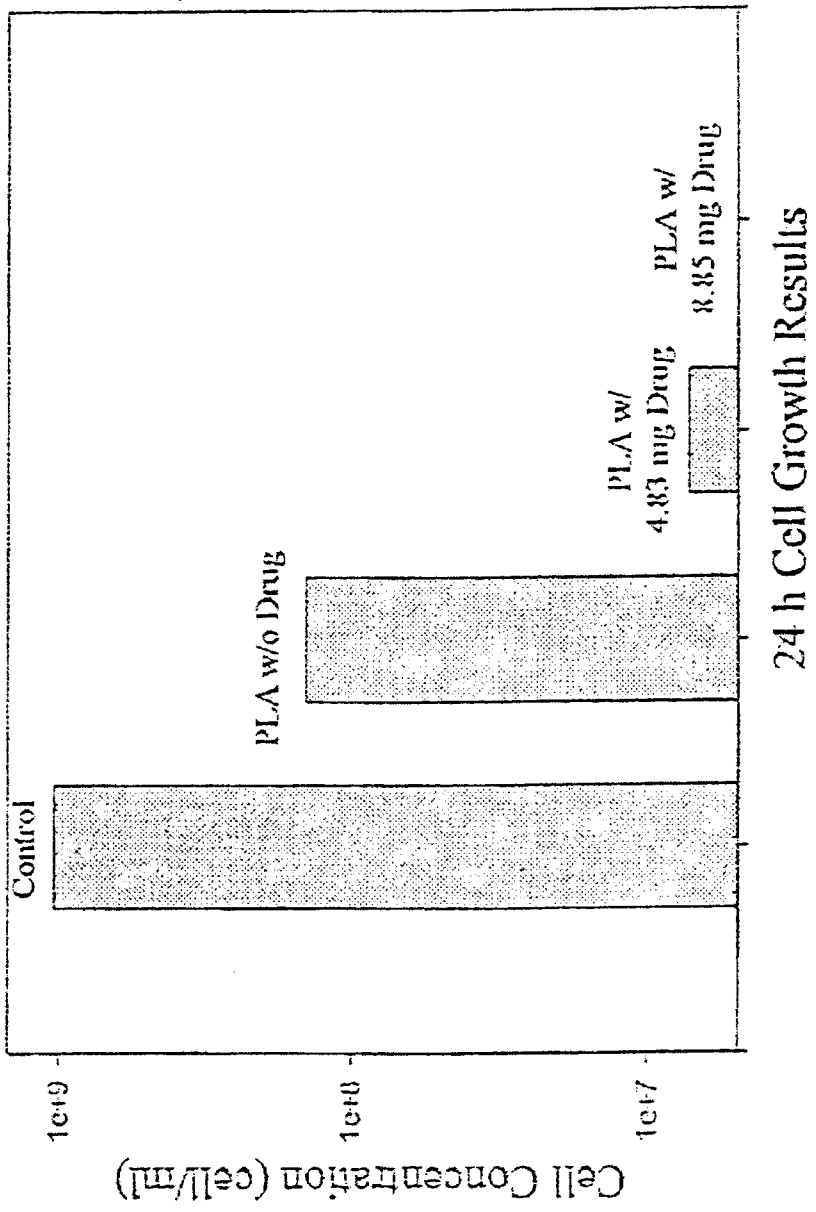

Antibacterial test results of PLA membrane
Cell Concentration (cell/ml)
1e+9
1e+8
1e+7
Control
PLA w/o Drug
PLA w/ 4.83 mg Drug
PLA w/ 8.85 mg Drug
24 h Cell Growth Results

FIG-17

In-vivo degradation after a week

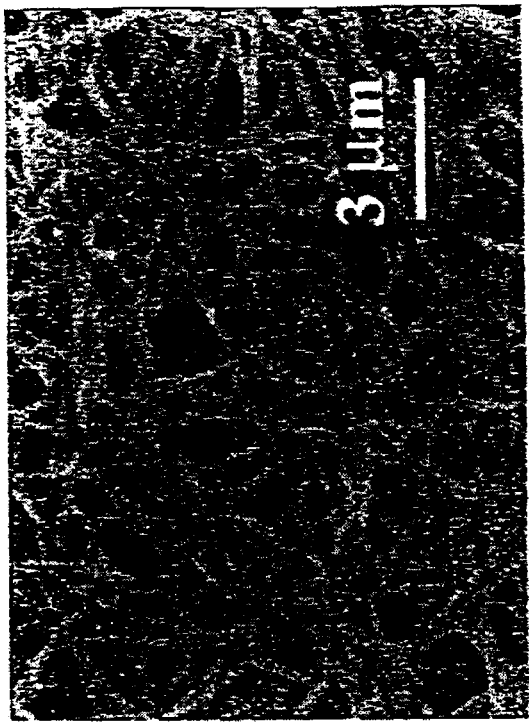
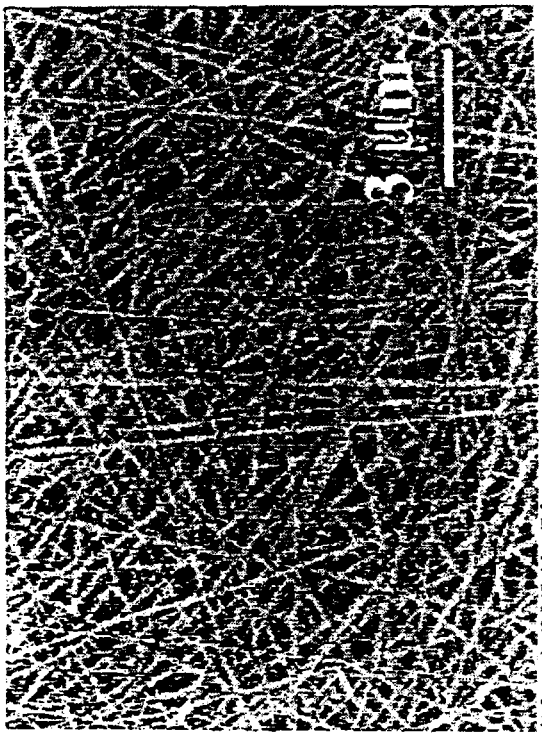


FIG-16

SEM image of as-spun membrane



BIODEGRADABLE AND/OR BIOABSORBABLE FIBROUS ARTICLES AND METHODS FOR USING THE ARTICLES FOR MEDICAL APPLICATIONS

This application is a Divisional of Ser. No. 09/859,007 filed on May 16, 2001.

BACKGROUND OF INVENTION

The present invention relates to biodegradable and/or bioabsorbable fibrous articles. More specifically, the present invention is directed to products and methods having utility in medical applications. In one embodiment, the fibrous articles of the invention are polymeric membranes.

Polymeric membranes produced by an electrospinning technique have been suggested as being useful for biological membranes such as substrates for immobilized enzymes and catalyst systems, wound dressing materials and artificial blood vessels, as well as for aerosol filters and ballistic garments.

Electrospinning is an atomization process of a conducting fluid which exploits the interactions between an electrostatic field and the conducting fluid. When an external electrostatic field is applied to a conducting fluid (e.g., a semi-dilute polymer solution or a polymer melt), a suspended conical droplet is formed, whereby the surface tension of the droplet is in equilibrium with the electric field. Electrostatic atomization occurs when the electrostatic field is strong enough to overcome the surface tension of the liquid. The liquid droplet then becomes unstable and a tiny jet is ejected from the surface of the droplet. As it reaches a grounded target, the material can be collected as an interconnected web containing relatively fine, i.e. small diameter, fibers. The resulting films (or membranes) from these small diameter fibers have very large surface area to volume ratios and small pore sizes. However, no practical industrial process has been implemented for producing membranes useful for medical applications. This is because with the production of small fibers, such as nanosize fibers, the total yield of the process is very low and a scale-up process, which maintains the performance characteristics of the films (or membranes), cannot be easily achieved.

U.S. Pat. No. 4,323,525 is directed to a process for the production of tubular products by electrostatically spinning a liquid containing a fiber-forming material. The process involves introducing the liquid into an electric field through a nozzle, under conditions to produce fibers of the fiber-forming material, which tend to be drawn to a charged collector, and collecting the fibers on a charged tubular collector which rotates about its longitudinal axis, to form the fiberous tubular product. It is also disclosed that several nozzles can be used to increase the rate of fiber production. However, there is no suggestion or teaching of how to control the physical characteristics of the tubular product, other than by controlling the charge and rotation speed of the tubular collector. It is further noted that the spinning process of the '525 patent is used to fabricate tubular products having a homogenous fiber matrix across the wall thickness.

U.S. Pat. No. 4,689,186 is directed to a process for the production of polyurethane tubular products by electrostatically spinning a fiber-forming liquid containing the polyurethane. It is disclosed that auxiliary electrodes can be placed around the collector to help facilitate collection of the fibers. It is disclosed that the auxiliary electrodes can be arranged to facilitate separation or to prevent adhesion of the formed fibers. There is no teaching or suggestion of independently controlling jet formation, jet acceleration and fiber collection. It is also noted that the spinning process of the '186 patent is used to fabricate tubular products having a homogenous fiber matrix across the wall thickness.

In one aspect, the present invention is directed to products and methods for preventing the formation of post-surgical adhesions between a healing trauma site and adjacent surrounding tissue.

Adhesion formation is a natural and inevitable consequence of surgery. Injury, surgical incisions, abrasion or other operative damage to the peritoneum, pleural or abdominal cavity results in an outpouring of a serosanguinous exudate. This exudate can accumulate on the injured surface and subsequently coagulate, producing fibrinous bands between abutting surfaces which can become organized by fibroblast proliferation to become collagenous adhesions. Adhesions are also known to form at bone fracture sites resulting in adhesions between the bone fracture surface and the surrounding tissue.

Adhesions can lead to serious complications. For example, adhesions that form in relation to intestinal surgery such as bowel resection, hernia repair, etc., may cause obstruction of the intestine. Adhesions that form near a bone fracture site may reduce or hinder the normal movement of the area of repair by restricting the natural movement of tendons over the adjacent bone. Adhesions may also form in the vicinity of nerves and disrupt nerve transmissions with a resultant diminution of sensory or motor function. Adhesions have also been known to lead to female infertility, chronic debilitating pain and difficulty with future operations. Typically, a patient will often have to undergo additional surgery to remove adhesions, only to have them reform.

Various methods and substances have been used in the hope of preventing post-operative adhesions. Certain drugs and surfactants have been suggested. For example, U.S. Pat. No. 4,911,926 is directed to adhesion prevention by application of aqueous and non-aqueous compositions of a polyoxyalkylene block copolymer to injured areas of the peritoneal or pleural cavity or organs situated therein subsequent to surgical injury.

Other surgical adjuvants have been used in an attempt to minimize or prevent adhesions following surgery, including anti-inflammatory drugs (such as corticosteroids) to decrease vascular permeability, antihistamines to reduce fibroblast proliferation, anticoagulants (such as heparin) and antibiotics (such as vibramycin or metokin) to reduce the incidence of infection. However, the use of drugs or compositions which are applied to the surgical area have only had limited success in preventing adhesions.

Another approach to adhesion prevention involves application of a physical barrier at the area of surgical injury. The theory is that a mechanical barrier, placed between the injured, healing serosal surfaces, which persists until all serosal healing has taken place will prevent adhesions and the sequela, e.g., small bowel obstruction. Bioabsorbable materials in the form of barrier layers to prevent adhesions of tissues which have been suggested include products based on cellulose materials. However, the use of commercial cellulose based products to prevent adhesions has certain drawbacks. For example, the performance in preventing adhesions is limited. Furthermore, certain products have been reported to have handling problems during surgery or can cause scars after use.

U.S. Pat. No. 4,674,488 is directed to interposing a barrier layer of soft biological tissue, such as collagen, collagen-

fabric films, collagen membranes, or reconstituted collagen or Dacron™, mesh, at the interface of a bone fracture and the surrounding tissue. U.S. Pat. No. 4,603,695 is directed to a molded polymeric material for preventing adhesion of vital tissues. The polymeric material is made of a biodegradable and absorbable polymer such as certain polyesters, collagen, amino acid polymers and chitin and may be placed where there is a possibility of adhesion setting in. Although biological materials, such as collagen, are generally "biocompatible," they can generate scars when implanted in certain forms, and it is difficult to precisely control the degradation of such materials.

Other materials have also been used to form physical barriers in an attempt to prevent adhesions, including silicone elastomers, gelatin films and knit fabrics of oxidized regenerated cellulose (hereinafter ORC). In some cases, it is suggested that heparin, heparinoid, or hexuronyl hexosaminogly can be incorporated into the matrix of an ORC fabric or other matrices of hyaluronic acid, cross-linked and uncross-linked collagen webs, synthetic resorbable polymers, gelatin films, absorbable gel films, oxidized cellulose fabrics and films which are fabricated into a form that is said to be drapable, conformable and adherent to body organs and substantially absorbable within 30 days. See, e.g., U.S. Pat. No. 4,840,626 or EPA Publication No. 0 262 890 or EPA Publication No. 0 372 969. However, as discussed above, it is difficult to precisely control the degradation rate of many of these materials and scar tissue can result from use of many of the materials.

Physical barriers are also used to cover and protect wound sites. PCT/US91/08972 is directed to a surgical article having a bioabsorbable fibrous matrix in a laminar relationship with a bioabsorbable cell barrier sheet. U.S. Pat. No. 5,092,884 and EPA Publication No. 0 334 046 are directed to a surgical composite structure having absorbable and non-absorbable components which may be useful for repairing anatomical defects, e.g., preventing hernia formation in an infected area. The nonabsorbable portion of the composite acts as a reinforcement material. The growth of natural tissue is said to be enhanced by controlled degradation of the absorbable portion. U.S. Pat. No. 5,035,893 relates to a wound covering composition having a sheet of biopolymeric material and a film of polyurethane resin. An antibacterial agent may be provided between the polyurethane film and the sheet of biopolymeric material, thereby forming a three-layer wound covering material. With the cure of the wound, it is said that the biopolymeric material is taken in as living tissue and the polyurethane film can be peeled off from the sheet without hurting the surface of a wound. Again, the use of many biopolymeric materials can result in the formation of scar tissue.

Thus, there is a need for improved membranes and other fibrous articles, which can be produced on an industrial scale, and for improved products and methods for reducing the formation of post-surgical adhesions, as well as for other medical applications, which do not have the above-mentioned disadvantages.

SUMMARY OF INVENTION

According to the present invention, it has now been found that biodegradable and/or bioabsorbable articles, e.g. membranes, having improved performance and handling characteristics for medical applications can be provided without the above-mentioned disadvantages.

In one aspect, the invention relates to a biodegradable and/or bioabsorbable fibrous article formed by electrospinning fibers of biodegradable and/or bioabsorbable fiberizable material, in which the article contains a composite of different biodegradable and/or bioabsorbable fibers.

In another aspect, the invention relates to a biodegradable and/or bioabsorbable fibrous article formed by electrospinning fibers of biodegradable and/or bioabsorbable fiberizable material, in which the article contains an asymmetric composite of different biodegradable and/or bioabsorbable fibers.

Different fibers can include fibers of different diameters, fibers of different biodegradable and/or bioabsorbable materials, or fibers of both different diameters and different biodegradable and/or bioabsorbable materials.

Preferably, the article will contain at least about 20 weight percent of submicron diameter fibers, more preferably, the article will contain at least about 50 weight percent of submicron diameter fibers.

Preferably, the biodegradable and/or bioabsorbable fiberizable material is a biodegradable and/or bioabsorbable polymer. The biodegradable and/or bioabsorbable polymer preferably contains a monomer selected from the group consisting of a glycolide, lactide, dioxanone, caprolactone, trimethylene carbonate, ethylene glycol and lysine.

In one embodiment the biodegradable and/or bioabsorbable polymer contains a biodegradable and/or bioabsorbable linear aliphatic polyester, more preferably a polyglycolide or a poly(glycolide-co-lactide) copolymer.

In another embodiment the biodegradable and/or bioabsorbable fiberizable material contains a material derived from biological tissue, e.g., collagen, gelatin, polypeptides, proteins, hyaluronan acid and derivatives or synthetic biopolymers.

The fibers of different biodegradable and/or bioabsorbable materials can include fibers having different chemical composition, such as different polymeric materials, different molecular weights of the same polymeric material, different blends of polymers, materials having different additives or materials having different concentration of additives.

In another embodiment the article will contain different fibers, i.e. different diameters and/or different materials, having diameters in the range from a few nanometers up to almost about one micron, more preferably about 10 up to about 1000 nanometers and most preferably from about 20 to about 500 nanometers. The fibers of different diameters can include both fibers having diameters less than 300 nanometers and fibers having diameters greater than 300 nanometers.

The article can also contain small blobs of biodegradable and/or bioabsorbable material. Preferably, the small blobs will have diameters in the range of about 20 to about 500 nanometers and, more preferably, about 200 to about 1500 nanometers.

In one embodiment, the article also contains at least one medicinal agent. The medicinal agent can be contained within the biodegradable and/or bioabsorbable material itself, including within the fibers or within the small blobs of material, if present. In such a case, the fibers (and/or small blobs) can contain different concentrations of the medicinal agent or different medicinal agents.

The article can also have the structure of a plurality of layers, wherein at least one of the layers is a composite (or asymmetric composite) of different biodegradable and/or bioabsorbable fibers. In such a case, the article can also contain at least one medicinal agent between at least two of the layers.

In one embodiment, the above described fibrous articles are in the form of a membrane.

The membrane according to the invention will preferably have a thickness in the range of about 10 to about 5000 microns, more preferably about 20 to about 1000 microns.

In another aspect, the invention relates to a fibrous article formed by electrospinning different fibers of different materials, in which the article contains a composite of different fibers containing fibers of at least one biodegradable material and fibers of at least one non-biodegradable material. Preferably, the compositite of different fibers will contain submicron diameter fibers. The composite can be an asymmetric composite.

In another aspect, the invention is directed towards an adhesion-reducing barrier containing a biodegradable and/or bioabsorbable membrane, in which the membrane contains:

a composite of different biodegradable and/or bioabsorbable fibers; or

an asymmetric composite of different biodegradable and/or bioabsorbable fibers.

Preferably, the adhesion-reducing barrier contains the above described membranes.

In yet another aspect, the invention is directed to a method for reducing surgical adhesions which involves positioning an adhesion-reducing barrier between the site of surgical activity and neighboring tissues. The barrier contains a biodegradable and/or bioabsorbable membrane, in which the membrane contains:

a composite (or an asymmetric composite) of different biodegradable and/or bioabsorbable fibers;

a plurality of layers, with at least two layers having different biodegradable and/or bioabsorbable fibers from each other; or

sub-micron diameter biodegradable and/or bioabsorbable fibers, having at least one medicinal agent contained within the fibers.

Preferably, the method involves use of the above described barriers.

In yet another aspect, the invention is directed to a system for controlled delivery of a medicinal agent which contains the medicinal agent to be delivered and a biodegradable and/or bioabsorbable fibrous article physically associated with the medicinal agent to release the agent at a controlled rate. The article contains a composite of different biodegradable and/or bioabsorbable fibers or an asymmetric composite of different biodegradable and/or bioabsorbable fibers.

Preferably, the system will include the articles and biodegradable and/or bioabsorbable materials discussed above.

In another aspect, the invention is directed to a method for the controlled delivery of a medicinal agent which involves implanting at a target site in an animal, a system for controlled delivery of a medicinal agent. The system for controlled delivery of a medicinal agent contains the medicinal agent to be delivered and a biodegradable and/or bioabsorbable fibrous article physically associated with the medicinal agent to release the agent at a controlled rate. The article contains a composite of different biodegradable and/or bioabsorbable fibers or an asymmetric composite of different biodegradable and/or bioabsorbable fibers.

Preferably, the method involves use of the above described system.

The present invention provides biodegradable and/or bioabsorbable fibrous articles, e.g. membranes, having improved performance and handling characteristics for medical applications, including improved performance in preventing adhesions. The invention also provides fibrous articles containing fibers of controlled size and having controlled morphology and biodegradation rate with utility in a controlled delivery system.

Additional objects, advantages and novel features of the invention will be set forth in part in the description and examples which follow, and in part will become apparent to those skilled in the art upon examination of the following, or may be learned by practice of the invention. The objects and advantages of the invention may be realized and attained by means of the instrumentalities and combinations particularly pointed out in the appended claims.

BRIEF DESCRIPTION OF THE FIGURES

FIG. **1** is a schematic of an electrospinning system.

FIG. **2** is a schematic of an array of spinnerets for an electrospinning process.

FIG. **3**(*a*) is a side view schematic of a multiple spinneret system for producing membranes in accordance with the invention.

FIG. **3**(*b*) is a cross-sectional view of the spinneret system of FIG. **3**(*a*) as seen along viewing lines IV—IV thereof.

FIG. **3**(*c*) is a bottom view of the multiple spinneret system of FIG. **3**(*a*).

FIG. **4** is an SEM of a PLA-co-PGA membrane spun from a solution containing 1 wt % KH_2PO_4.

FIG. **5** is an SEM of a PLA-co-PGA membrane spun from a solution without salt added.

FIG. **6** is an SEM of a membrane described in Example 1.

FIG. **7** is an SEM of a membrane described in Example 4.

FIG. **8** is a graph of the results of the drug release test described in Example 4.

FIG. **9** is an SEM of a PLA membrane described in Example 5.

FIG. **10** is a graph of the results of the biodegradation tests described in Example 6.

FIG. **11** is an SEM of the PLA membrane described in Example 7.

FIG. **12** is an SEM of the PLA membrane described in Example 7 after 1 week of degradation.

FIG. **13** is a graph of the results of the adhesion experiment described in Example 8.

FIG. **14** is a graph showing the tensiometer readings from the experiment described in Example 8.

FIG. **15** is a graph of the results of the antibacterial test described in Example 9.

FIG. **16** is an SEM of the as spun membrane described in Example 10.

FIG. **17** is an SEM of the partially biodegraded membrane described in Example 10.

DETAILED DESCRIPTION OF THE INVENTION

The present invention is directed to biodegradable and/or bioabsorbable fibrous articles and methods for using the articles for medical applications including reducing the formation of post-surgical adhesions between a healing trauma site and the adjacent tissue and controlled delivery systems.

In one aspect, the invention relates to a biodegradable and bioabsorbable fibrous article formed by electrospinning

fibers of biodegradable and/or bioabsorbable fiberizable material in which the article contains a composite of different biodegradable and/or bioabsorbable fibers.

In another aspect, the article can contain an asymmetric composite of different biodegradable and/or bioabsorbable fibers.

In yet another aspect, the article can also include fibers of at least one non-biodegradable/non-bioabsorbable material.

By the term biodegradable is intended a material which is broken down (usually gradually) by the body of an animal, e.g. a mammal, after implantation.

By the term bioabsorbable is intended a material which is absorbed or resorbed by the body of an animal, e.g. a mammal, after implantation, such that the material eventually becomes essentially non-detectable at the site of implantation.

By the terminology "biodegradable and/or bioabsorbable fiberizable material" is intended any material which is biocompatible, as well as biodegradable and/or bioabsorbable, and capable of being formed into fibers, as described more fully below. The material is also capable of being formed into a fibrous article which is suitable for implantation into an animal and capable of being biodegraded and/or bioabsorbed by the animal.

The biodegradable and/or bioabsorbable fiberizable material is preferably a biodegradable and bioabsorbable polymer. Examples of suitable polymers can be found in Bezwada, Rao S. et al. (1997) *Poly(p-Dioxanone) and its copolymers, in Handbook of Biodegradable Polymers*, A. J. Domb, J. Kost and D. M. Wiseman, editors, Hardwood Academic Publishers, The Netherlands, pp. 29–61, the disclosure of which is incorporated herein by reference in its entirety.

In a preferred embodiment the biodegradable and/or bioabsorbable polymer contains a monomer selected from the group consisting of a glycolide, lactide, dioxanone, caprolactone, trimethylene carbonate, ethylene glycol and lysine. By the terminology "contains a monomer" is intended a polymer which is produced from the specified monomer(s) or contains the specified monomeric unit(s). The polymer can be a homopolymer, random or block co-polymer or hetero-polymer containing any combination of these monomers. The material can be a random copolymer, block copolymer or blend of homopolymers, copolymers, and/or heteropolymers that contains these monomers.

In one embodiment, the biodegradable and/or bioabsorbable polymer contains bioabsorbable and biodegradable linear aliphatic polyesters such as polyglycolide (PGA) and its random copolymer poly(glycolide-co-lactide) (PGA-co-PLA). The FDA has approved these polymers for use in surgical applications, including medical sutures. An advantage of these synthetic absorbable materials is their degradability by simple hydrolysis of the ester backbone in aqueous environments, such as body fluids. The degradation products are ultimately metabolized to carbon dioxide and water or can be excreted via the kidney. These polymers are very different from cellulose based materials, which cannot be absorbed by the body.

These materials are also effective drug carriers for pharmaceutical products, as they meet several drug release criteria including a biocompatible and biodegradable polymer matrix that provides efficient drug loading. The degradation rate of these materials, as well as the release rate of entrapped drugs, can only be roughly controlled by varying the molecular structure and the molecular weight as there is no linear relationship between the physical properties of the constituent homopolymers or their copolymers. However, by controlling the filament diameter (to nanometer sizes) and the assembly morphology as described more fully below, the degradation rate and the drug release rate can be finely tuned. For example, Dunne et al. examined the influence of processing conditions, particle characteristics and media temperature on the degradation of PGA-co-PLA spherical particles. They found that a linear relationship between the degradation rate and particle size existed, with the larger particles degrading fastest.

Other examples of suitable biocompatible polymers are polyhydroxyalkyl methacrylates including ethylmethacrylate, and hydrogels such as polyvinylpyrrolidone, polyacrylamides, etc. Other suitable bioabsorbable materials are biopolymers which include collagen, gelatin, alginic acid, chitin, chitosan, fibrin, hyaluronic acid, dextran, polyamino acids, polylysine and copolymers of these materials. Any combination, copolymer, polymer or blend thereof of the above examples is contemplated for use according to the present invention. Such bioabsorbable materials may be prepared by known methods.

Particularly useful biodegradable and/or bioabsorbable polymers include poly-lactides, poly-glycolides, polycarprolactone, polydioxane and their random and block copolymers. Examples of specific polymers include poly D,L-lactide, polylactide-co-glycolide (85:15) and polylactide-co-glycolide (75:25).

Preferably, the biodegradable and/or bioabsorbable polymers used in the articles of the present invention will have a molecular weight in the range of about 1,000 to about 8,000,000 g/mole, more preferably about 4,000 to about 250,000 g/mole.

By the terminology "composite of different biodegradable and/or bioabsorbable fibers" is intended any combination of the different fibers interleaved with each other in the form of a fibrous matrix, which can be in the form of a membrane or other three dimensional form of tailored geometry, such as a tube, rod or plug.

By the terminology "asymmetric composite of different biodegradable and/or bioabsorbable fibers" is intended a composite of different biodegradable and/or bioabsorbable fibers, having at least one of non-homogeneous porosity or assembled morphology, variations in the ratio of different fibers, progressing through different regions of the composite material. For example, with reference to a membrane containing an asymmetric composite of different biodegradable and/or bioabsorbable fibers, the porosity, morphology or variations in fibers can be varied either in a direction perpendicular to or parallel with the surface of the membrane. Thus, an asymmetric composite of different biodegradable and/or bioabsorbable fibers can have 100 percent submicron diameter fibers on a first side of the membrane, zero percent submicron diameter fibers on the opposite side, and a progressively lower percentage of submicron diameter fibers in the direction from the first side across the thickness of the membrane.

By the terminology "different biodegradable and/or bioabsorbable fibers" is intended to include fibers of different diameters, fibers of different biodegradable and/or bioabsorbable materials, or fibers of both different diameters and different biodegradable and/or bioabsorbable materials.

By the terminology "fibers of different diameters" is intended that the article will include fibers having at least two different target (or intended) diameters.

By the terminology "fibers of different biodegradable and/or bioabsorbable materials" is intended to include fibers

having different chemical composition, in the form of, for example, different polymeric materials, different molecular weights of the same polymeric material, or different additives (or concentration of additives), such as medicinal agents.

In one embodiment, the article will contain different fibers having diameters in the range from a few up to about 1,000 nanometers, more preferably about 10 up to about 1000 nanometers and most preferably about 20 to about 500 nanometers.

The article can contain fibers having different diameters with a controlled percentage of sub-micron diameter fibers. Preferably, the article will contain at least about 10 wt % of sub-micron diameter fibers, more preferably at least about 20 wt %, and most preferably at least about 50 wt %.

Optionally, the fibrous article can contain at least one medicinal agent. In such a case, one or more medicinal agents may be incorporated into the fibers of the article. Preferably, the medicinal agent(s) will be mixed with the bioabsorable material, e.g., polymer, prior to formation of the fibers.

In loading the medicinal agent, the medicine may need to be dissolved in a solvent that may not be compatible with the solvent used in the electrospinning process. A block copolymer, acting as a surfactant, can then be used to circumvent this difficulty. One block that forms the micellar shell is a polymer that is compatible with the fibrous material that will be used to form the nano-fibers and the other block that has a different chemical composition is more compatible with the medicinal agent. For example, a block copolymer of PLA-co-PEO could form a micelle that is compatible with the PLA solution while the inner PEO core that is more hydrophilic can be used to load more hydrophilic medicinal agents. The micellar property and uptake capacity can be determined by the chemical composition of the blocks, the molecular architecture, the block length, and the chain length ratio of the blocks. The micelles, being compatible with the fibrous material can be incorporated into the nano-fibers during processing. Furthermore, the drug release rate can also be controlled by the micellar property. For example, a glassy core can reduce the drug release rate.

By the term "medicinal agent" is intended any substance or mixture of substances which may have any clinical use in medicine. Thus medicinal agents include drugs, enzymes, proteins, peptides, glycoproteins, hormones or diagnostic agents such as releasable dyes or tracers which may have no biological activity per se, but are useful for diagnostic testing, e.g., MRI.

Examples of classes of medicinal agents that can be used in accordance with the present invention include antimicrobials, analgesics, antipyretics, anesthetics, antiepileptics, antihistamines, anti-inflammatories, cardiovascular drugs, diagnostic agents, sympathomimetic, cholinomimetic, antimuscarinics, antispasmodics, hormones, growth factors, muscle relaxants, adrenergic neuron blockers, anti-neoplastics, immunosuppressants, gastrointestinal drugs, diuretics, steroids and enzymes. It is also intended that combinations of medicinals can be used in accordance with the present invention.

Thus, in one embodiment of the present invention focal delivery and application of a medicinal agent to the wound site is achieved. Focal application can be more desirable than general systemic application in some cases, e.g., chemotherapy for localized tumors, because it produces fewer side effects in distant tissues or organs and also concentrates therapy at intended sites. Focal application of growth factors, anti-inflammatory agents, immune system suppressants and/or antimicrobials by the membranes of the present invention is an ideal drug delivery system to speed healing of a wound or incision. Focal application of anesthetics by the articles of the present invention is an ideal drug delivery system for pain management.

In one embodiment, the above described fibrous articles are in the form of a membrane. Although the discussion that follows is directed to membranes in accordance with the invention, it should be understood that the discussion is applicable to other three dimensional articles, including, but not limited to tubes, rods, plugs, blocks, etc.

In one aspect the invention is directed to biodegradable and/or bioabsorbable membranes having a controlled biodegradation rate. The chemical composition, i.e., specific polymers or blends of polymers, the fiber diameter, the membrane morphology, the molecular weight distribution and the porosity of the membrane can be used to control the degradation and/or absorption time for the membrane. As such, the membranes containing medicinal agents within the fibers themselves are well suited as a controlled drug delivery device, since the above-mentioned factors can also be used to control the rate of release of the medicinal agent.

The membrane can also contain a plurality of fibers which have different medicinal agents or different concentrations of medicinal agents. Such membranes offer unique treatment options with combinations of medicinal agents and release profiles.

In one embodiment, the membrane can contain a plurality of biodegradable and/or bioabsorable non-woven layers. The layers can have the same or different chemical composition, fiber diameters, membrane morphology and porosity as discussed more fully above. Multiple layered membranes can offer yet another way to precisely control degradation and drug release rate.

In such an embodiment, it is also contemplated that medicinal agents can be incorporated between the layers of the multi-layered membrane, instead of or in addition to, incorporating the agents into the fiber structure itself.

In one embodiment, the membrane can be attached to a non-absorbable reinforcement layer, such as a Marlox mesh.

In another aspect, the invention relates to a fibrous article formed by elecrospinning different fibers of different materials, in which the article contains a composite of different fibers containing fibers of at least one biodegradable material and fibers of at least one non-biodegradable material.

In addition to drug delivery devices, the membranes of the present invention are particularly well suited for use as an adhesion-reducing barrier.

The membranes of the present invention may be employed as barriers between tissues or barriers between tissue and bone to prevent binding of tissue to tissue or of tissue to bone. Examples of uses of the devices of the present invention include, but are not limited to, barriers between the internal female reproductive organs (e.g., uterus, fallopian tubes, ovaries); barriers between the internal female reproductive organs and the peritoneum; barriers for use during laparoscopy; barriers between periodontal tissue; barriers between cartilage or between cartilage and bone; barriers between digestive organs; spinal barriers; barriers between digestive organs and peritoneum; barriers between the epicardium and surrounding structures such as the pericardium, mediastinal fat, pleura, and sternum; barriers between tendons and tendon sheaths, such as those in the wrist and ankle; bone fracture wraps; barriers between

muscle tissue and bone; barriers between the esophagus and mediasternum; barriers between the gall bladder or pancreas and the peritoneum; and barriers for scrotal surgery.

The membranes of the present invention may also be used for guided tissue regeneration. For example, the membranes may be used to cover internal perforations, such as, for example, perforations in blood vessels, internal organs, the nasal septum, and the eardrum membrane, and may be used to reconstruct the abdominal wall, or to reinforce areas prone to or showing scar formation, such as, for example, inguinal hernias. The membrane therefore acts as a patch for covering the perforation until complete healing, followed by copolymer absorption, is achieved. It is also contemplated that the membranes may be employed as a cover for burns, whereby the device acts as a patch until the burn is healed.

The membranes of the present invention may be employed as a scaffolding to treat ulcers. A porous membrane can be designed to stimulate the proliferation of fibrous tissue, as a consequence of which, for example, in the case of ulcers, the wound bed becomes more optimal for the regeneration of skin.

The membranes of the present invention may also be employed in redirect healing, whereby the devices are employed to protect nerves and organ coverings, and mucosa during the healing process, whereby the formation of fibrous tissue over such nerves, organs, and mucosa is prevented.

The membranes may also be employed to prevent the formation of internal blood clots after surgery or traumatic injury.

The membranes may also be employed in covering denuded epithelial surfaces or weakened areas such as damaged middle ear mucosa or other mucosal surfaces, thinned vascular walls, or surgically denuded areas, such as, for example, surgically denuded areas of the pelvis.

The membranes may also be employed as anti-fibroblastic growth barriers, or as nerve coaptation wraps for connecting or repairing severed nerve ends or for repairing inflamed nerves.

The membranes of the present invention may be formed or constructed into various shapes including, but not limited to, flat sheets, tubes, rods or other three dimensional articles, as necessary to facilitate use in a particular application.

A post surgical anti-adhesion barrier or membrane of the present invention is generally used in the form of a sheet of a desired size and shape. A surgeon may cut a custom shape from preformed sheets to suit particular applications. After the membrane is shaped for a suitable fit, the flexible nature of the membrane enables the surgeon to conform the membrane to fit around the area of injury. The membrane can be formed into a strip which wraps around the organ, e.g., an intestine, to prevent formation of adhesions. An anti-adhesion membrane according to the present invention can incorporate ties or straps which connect to the membrane and which are used to tie or otherwise secure the membrane to an area of injury. It is further contemplated that the anti-adhesion membranes of the present invention may be affixed to the wound site by surgical fasteners or sutures. The flexible nature of the present anti-adhesion membrane allows the membrane to flex and bend along with normal movements of the body without being overly restrictive.

Thus, the invention is also directed to a method for reducing post-surgical adhesions. The method involves positioning an adhesion-reducing barrier between the site of surgical activity and neighboring tissues. The adhesion-reducing barrier will contain a biodegradable and/or bioabsorbable membrane. The membrane is preferably the biodegradable and/or bioabsorbable membranes discussed above. The membrane can also be a biodegradable and/or bioabsorbable membrane which contains a plurality of layers, with at least two layers having different biodegradable and/or bioabsorbable fibers from each other or contains sub-micron diameter biodegradable and/or bioabsorbable fibers, having at least one medicinal agent contained within the fibers. Preferably, the membrane will contain an antibiotic.

All embodiments of surgical adhesion barriers or membranes as described herein are well-suited for application by techniques involving endoscopy. Endoscopic surgical procedures involve the use of cannulas or tubes which provide narrow openings into a body and allow minimally invasive access to surgical targets. In laparoscopic procedures, surgery is performed in the interior of the abdomen through small tubes inserted therein. Endoscopes are frequently used as viewing devices inserted through the cannulas which allow surgeons to see the interior of the body.

Certain endoscopic and laparoscopic procedures may require that the surgical region be insufflated. Accordingly, any instrumentation inserted into the body should be substantially sealed to ensure that gases do not enter or exit the body through the incision. Moreover, endoscopic and laparoscopic procedures often require the surgeon to operate on organs, tissues and/or vessels far removed from the incisions. Thus, instruments used in such procedures are typically long and narrow while being functionally controllable from a proximal end of the instrument.

In accordance with the present invention any apparatus for deploying and positioning any of the adhesion barriers or membranes disclosed herein may be inserted through a cannula and deposited at a target site. Once the barrier is positioned as desired, it may optionally be sutured, stapled or otherwise fastened to the target site with instruments designed to be inserted through a cannula.

Thus, in another aspect, the invention is directed to a method of reducing surgical adhesions which involves positioning an adhesion-reducing barrier between the site of surgical activity and neighboring tissue. More specific applications are discussed above.

Nanofiber Fabrication Technique for Biodegradable and/or Bioabsorbable Polymers: Electrospinning Membranes with Different Biodegradable and/or Bioabsorbable Fibers

The membranes according to the present invention are preferably produced by electrospinning using a multiple jet system. Preferably, the multiple jet system includes an array of spinnerets for introducing conducting fluid containing the biodegradable and/or bioabsrobable fiberizable material. The use of a multiple jet system to produce membranes in accordance with the invention is possible by having independent control over different jets. Thus, different jets can produce different fibers as discussed more fully above.

Moreover, sub-micron diameter fibers can be produced in accordance with the invention at a relatively high yield. For example, a 40% polymer solution being spun from a single spinneret with a diameter of 700 microns, which results in a final filament having a diameter of 250 nm, will have a draw ratio of 7.84×10^6. If the extrudate (conducting fluid) from each spinneret has a rate of about 10 μl/min, the final filament speed will be about 136 m/s for each spinneret, which is a relatively high spinning rate. Thus, a commercially viable process for making membranes according to the invention is achievable with a sufficient number of spinnerets operating at such speeds.

The conducting fluid will preferably include a solution of the polymer materials described more fully above. The polymer material used to form the membrane is first dissolved in a solvent. The solvent can be any solvent which is capable of dissolving the polymer and providing a conducting fluid capable of being electrospun. The solvent is preferably selected from N,N-Dimethyl formamide (DMF), tetrahydrofuran (THF), N-N-dimethyl acetamide (DMAc), methylene chloride, dioxane, ethanol, chloroform or mixtures of these solvents.

The conducting fluid can optionally contain a salt which creates an excess charge effect to facilitate the electrospinning process. Examples of suitable salts include NaCl, KH_2PO_4, K_2HPO_4,KIO_3, KCl, $MgSO_4$, $MgCl_2$, $NaHCO_3$, $CaCl_2$, or mixtures of these salts.

The polymer solution forming the conducting fluid will preferably have a polymer concentration in the range of about 1 to about 80 wt %, more preferably about 10 to about 60 wt %. The conducting fluid will preferably have a viscosity in the range of about 50 to about 2000 mPa·s, more preferably about 200 to about 700 mPa·s.

The electric field created in the electrospinning process will preferably be in the range of about 5 to about 100 kilovolts (kV), more preferably about 10 to about 50 kV. The feed rate of the conducting fluid to each spinneret (or electrode) will preferably be in the range of about 0.1 to about 1000 microliters/min, more preferably about 1 to about 250 microliters/min.

A particular apparatus for producing membranes according to the present invention, which uses a multiple jet electrospinning system, is shown schematically in FIG. **1**. Equipment not essential to the understanding of the invention such as heat exchangers, pumps and compressors and the like are not shown.

Referring now to FIG. **1**, the conducting fluid, which contains the biodegradable polymer, is supplied by a micro-flow pump system **1**. The conducting fluid preferably contains a biodegradable polymer, a solvent and a salt, e.g., 25 wt % PLA-DMF solution with 1 wt % KH_2PO_4. Optionally, one or more medicinal agents can be incorporated into the conducting fluid. The pump system **1** is linked to a computer **2** which controls the flow rate of the conducting fluid to selected spinnerets by controlling pressure or flow rate. The flow rate can be changed depending upon the speed of the support membrane **3** and the desired physical characteristics of the membrane, i.e., membrane thickness, fiber diameter, pore size, membrane density, etc.

The pump system **1** feeds the conducting fluid to a multiple jet system **4** that contains manifolds **5** having a bank of spinnerets **6**. A charge in the range of about 20 to about 50 kV is typically applied to the spinnerets by a high voltage power supply **7**. A hood **8** is positioned over the multiple jet system **4** to remove the solvent at a controlled evaporation rate.

A ground plate **9** is positioned below the multiple jet system **4** such that an electric field is created between the charged spinnerets **6** and the ground plate **9**. The electric field causes tiny jets of the conducting fluid to be ejected from the spinnerets and spray towards the ground plate **9**, forming small, e.g., sub-micron, diameter filaments or fibers.

A moving support **3** is positioned between the charged spinnerets **6** and the ground plate **9** to collect the fibers which are formed from the spinnerets and to from an interconnected web of the fibers. The support **3** moves in the direction from the unwind roll **10** to the rewind roll **11**.

The micro-flow control/pumping system is electrically isolated from the ground and is powered by an isolation transformer **12**.

The post-spinning processors **13** have the functions of drying, annealing, membrane transfer (for example, from a stainless steel mesh substrate to another substrate, e.g., a Malox mesh) and post conditioning.

Multiple jets with designed array patterns can be used to ensure the fabrication of uniform thickness of the membrane. Hood, heating and sample treatment chambers can also be included to control the solvent evaporation rate and to enhance the mechanical properties. The recovered thickness can be precisely controlled from tens of microns to hundreds of microns. While additional embodiments or modifications to the electrospinning process and apparatus are described below, a more detailed description of an apparatus and method for electrospinning polymeric fibers is set forth in co-pending, commonly owned patent application, Ser. No. 09/859,004, entitled "Apparatus and Methods for Electrospinning Polymeric Fibers and Membranes," filed on May 16, 2001 and incorporated herein for all purposes by reference.

Variation of Electric/Mechanical Properties of Conducting Fluid

The properties of the resulting membrane produced by electrospinning will be affected by the electric and mechanical properties of the conducting fluid. The conductivity of the macromolecular solution can be drastically changed by adding ionic inorganic/organic compounds. The magneto-hydrodynamic properties of the fluid depend on a combination of physical and mechanical properties, (e.g., surface tension, viscosity and viscoelastic behavior of the fluid) and electrical properties (e.g., charge density and polarizability of the fluid). For example, by adding a surfactant to the polymer solution, the fluid surface tension can be reduced, so that the electrostatic fields can influence the jet shape and the jet flow over a wider range of conditions. By coupling a pump system that can control the flow rate either at constant pressure or at constant flow rate, the effect of viscosity of the conducting fluid can be controlled.

Electrode Design

In another method for producing membranes according to the present invention, the jet formation process during electrospinning is further refined to provide better control over fiber size. Instead of merely providing a charged spinneret and a ground plate, a positively charged spinneret is still responsible for the formation of the polymer solution droplet and a plate electrode with a small exit hole in the center is responsible for the formation of the jet stream. This exit hole will provide the means to let the jet stream pass through the plate electrode. Thus, if the polymer droplet on the positively charged spinneret has a typical dimension of 2–3 mm and the plate electrode is placed at a distance of about 10 mm from the spinneret, a reasonable electrostatic potential can be developed. The short distance between the two electrodes implies that the electrostatic potential could be fairly low. However, the resultant electric field strength could be sufficiently strong for the electrospinning process. By varying the electric potential of individual spinnerets, the jet formation can be controlled and adjusted for individual spinnerets. Such an electrode configuration should greatly reduce the required applied potential on the spinnerets from typically about 15 kilovolts (kV) down to typically about 1.5 to 2 kV (relative to the ground plate potential). The exact spinneret potential required for stable jet formation will depend on the electric/mechanical properties of the specific conducting fluid.

Control of Jet Acceleration and Transportation

In another method for producing membranes according to the present invention, the jet stream flight of individual

spinnerets is also precisely controlled. The jet stream passing through the plate electrode exit hole is positively charged. Although this stream has a tendency to straightening itself during flight, without external electric field confinement the jet will soon become unstable in its trajectory. In other words, the charged stream becomes defocused, resulting in loss of control over the microscopic and macroscopic properties of the fluid. This instability can be removed by using a carefully designed probe electrode immediately after the plate electrode and a series of (equally) spaced plate electrodes. The electrode assembly (i.e., the probe electrode and the plate electrodes) can create a uniform distribution of electrostatic potential along the (straight) flight path. The acceleration potential is formed by placing the base potential of the spinneret at about +20 to +30 kV above the target (at ground potential) while the electrostatic potential of the probe electrode can be adjusted to slightly below the plate electrode base potential. The composite electrodes are capable of delivering the jet stream to a desired target area.

Jet Manipulation

In yet another method for producing membranes according to the present invention, individual jet streams can be focused by using an "Alternating Gradient" (AG) technique. The basic idea is to use two pairs of electrostatic quadrupole lenses. The second lens has the same geometric arrangement as the first lens with a reversed (alternate) electric gradient. The positively charged jet stream will be focused, for example, in the xz plane after the first lens and then be refocused in the xz plane after the second lens. It is noted that the z-direction represents the direction of the initial flight path. By applying an additional triangle-shaped waveform to the potential on one of the pairs of the quadrupole, the jet can be swept across the target area, allowing the control of the direction of the jet stream. Furthermore, with varying waveform of the 'sweep' potential, a desired pattern on the target can be formed.

Pattern Design by Electrospinning

In yet another method for producing membranes according to the present invention, reference will be made to FIG. **2**. In this method, the conducting fluid is introduced into the electrospinning process through an array of electrospinning spinnerets **20**. The array of electrospinning spinnerets are assembled in a matrix **21** that provides electrical isolation for the spinnerets, with each spinneret having two pairs (X and Y direction) of miniature scanning electrodes **22**. The spinneret **20** and the scanning electrodes **22** are electrically wired such that each individual polymer solution jet can be turned on and off and be steered to a finite size target area. As each spinneret **20** can be turned on/off independently by electricity, the response time will be relatively fast. Also, each spinneret **20** can deliver a different solution, e.g., each containing a different polymer or different drug or concentration of drug. A designed pattern can be obtained in the resultant membrane. This pattern can be precisely controlled by a computer and can be tailored for specific medical applications.

Multiple Jet Slit-Die Geometry

In another apparatus for producing membranes in accordance with the present invention, reference is made to FIGS. **3**(*a*)–**3**(*c*). In this apparatus, a multiple jet system **30** comprises an array of electrospinning spinnerets **31**, each spinneret **31** being defined by a slit **32** formed in a slit-die **33** that is coupled to high voltage to serve as an electrode disposed above the ground plate **34**. As shown in detail in FIG. **3**(*c*), the spinnerets **31** are each interconnected by selectively narrow slits **35**, such that each spinneret **31** is interconnected to a neighboring spinneret **31** by a slit **35**. The conducting fluid will not flow through the slits **35**, but will flow through each of the spinnerets **31** in a more robust manner.

The slit-die approach permits three distinct advantages that are not available by using individual spinnerets. (1) The slit-die is made up of two separate components with controlled dimensions of the effective openings for the spinnerets. In other words, by changing the distance between the two components, the effective openings of the spinnerets become available. (2) The presence of slits between the larger openings permits fluid flow and thereby equalizes the pressure difference between the spinnerets. (3) The presence of slits can also reduce potential blockage of the fluid.

The membranes produced by the slit-die approach can achieve a larger degree of flexibility in the structures. For example, different size nanofibers can be produced from the same slit-die setup.

Control of Degradation Rate Through Processing Parameters

As discussed above, very different fiber diameter and morphology in the membrane can be obtained by changing the parameters in the electrospinning process. As the degradation rate is inversely proportional to the fiber diameter, the manipulation capability through processing parameters provides not only the means to control the degradation rate of the membrane but also the ways to control drug loading efficiency and the drug release rate.

For example, it is believed that a change in charge density (through the addition of salts) can significantly affect the fiber diameter. When 1 wt % potassium phosphate (KH_2PO_4) was added to a PLA-co-PGA solution, the fiber diameter became much thinner (see SEM picture in FIG. **4**) than the one with no salt added (FIG. **5**). Thus, it is believed that higher excess charge density generally favors the production of thinner fibers and lower excess charge density favors the production of thicker fibers. Several other kinds of salts (e.g. NaCl, KH_2PO_4, KIO and K_3PO_4), which are all biologically compatible to the body, are also contemplated.

Control of Drug Release Rate and Test of Antibacterial Effect

It is also believed that when a drug is incorporated into the fibers of the membrane, the drug release rate is a function of fiber diameter. As such, the release rate of a drug trapped in the membrane can be precisely controlled. Many surgical procedures often lead to adhesion formation involving the colon and rectum. This additionally increases the risk of post-operative infection. The addition of antibiotics to the membrane with scheduled release may be used to reduce the risk of abscess and infection.

EXAMPLES

The following non-limiting examples have been carried out to illustrate preferred embodiments of the invention. These examples include the preparation of membranes according to the invention, analysis of the membranes and testing of the membranes.

Example 1

A membrane was prepared as follows: a 30 wt % PLG copolymer/DMF solution was prepared by slowly dissolving PLG copolymer pellets (inherent viscosity of 0.55–0.75. Birmingham Polymers Inc., AL) into an N,N-dimethyl formamide (DMF) solvent at room temperature. The solution was then loaded into the 5 ml syringe fitted with a gauge 20

needle, and delivered through a Teflon tube (0.03" ID) to the exit hole of an electrode having a diameter of 0.025". The solution was pumped and controlled by a syringe pump (Harvard Apparatus "44" series, MA) at a flow rate of 20 microliters/min. A 25 kV positive high voltage (by Glassman High Voltage Inc.) was applied on the electrode. The distance from the tip of the electrode to the grounded collecting plate was 15 cm. A tiny electrospinning jet was formed and stabilized in 30 seconds under these conditions. The collecting plate was movable and controlled by a stepper motor. The collecting plate was continually moved at a rate of 1 mm/sec until a membrane having a relatively uniform thickness of about 100 microns was obtained. An SEM (Scanning Electron Microscopy) image of the membrane is shown in FIG. **6**.

Example 2

A biodegradable and bioabsorbable membrane according to the present invention, fabricated by a multi-jet electrospinning process, was prepared as follows: an 8 wt % polyacrylonitrile (Aldrich Chemical Company, Inc.)/DMF solution was prepared by slowly adding and dissolving the polymer powders into an organic solvent, which was DMF (N,N-dimethyl formamide), at room temperature. After the solution was completely mixed, it was then loaded into 6 individual syringes, each with a volume of 5 mL. The syringes were fitted with gauge 20 needles and the solution was delivered through Teflon tubes (0.03" ID) to 6 electrodes, each having a tiny hole with a diameter of 0.025". The polymer solution was finally pumped and controlled by a syringe pump (Harvard Apparatus "44" series, MA) at a flow rate of 25 microliters/min. In addition, a 26 kV positive high voltage (by Glassman High Voltage Inc.) was applied on the electrodes in order to obtain the existence of six well-stabilized electrospinning jets. The distance from the tip of the electrodes to the grounded collecting plate was 15 cm and the tips of the electrodes were spaced about 2 cm apart from each other. Closer spacing between electrodes (spinnerets) could have been achieved by changing appropriate parameters, e.g., by increasing the applied electric potential. The collecting plate was movable and controlled by a step motor. The collecting plate was continually moved at a rate of 1 mm/sec until a bioabsorable and biodegradable membrane having a relatively uniform thickness of about 100 microns was obtained.

Example 3

A polymer solution suitable for electrospinning, which contained a drug, was prepared as follows: A sample of Poly(DL-lactide) ("PLA") purchased from Birmingham Polymers, Inc., Birmingham, Ala. (Product No. D98120) having a weight average molecular weight of 1.09×10^5 g/mole and a polydispersity of 1.42 was stored in a vacuum oven at room temperature. The pellets were dissolved in DMF purchased from Fisher Scientific, Fair lawn, N.J. to form a 25 wt % solution. The antibiotic drug used was Mefoxin™ from Merck & Co., Inc., West Point, Pa. The antibiotic was dissolved in distilled water and then mixed with PLA/DMF solution in appropriate amounts to form the solution with a PLA/drug ratio of 9:1. A stable jet was formed using this solution in the electrospinning process described in Example 1.

Example 4

A second membrane was prepared in a similar manner to Example 1, except that a drug solution was added to the polymer solution prior to electrospinning and the voltage applied to the electrode was adjusted. The drug solution was prepared by dissolving 0.6 grams of Mefoxin (Merck & Co Inc.) into 0.4 grams of water. The drug solution was then very slowly (dropwise) added to the polymer solution with gentle stirring until it reached a final PLG/drug ratio of 19:1. A 20 kV positive high voltage (by Glassman High Voltage Inc.) was applied on the electrode. All other parameters were the same as Example 1. An SEM (Scanning Electron Microscopy) image of the membrane containing the drug is shown in FIG. **7**.

The drug release rate was determined by placing the membrane in a phosphate buffer solution (PBS) and then by monitoring the drug concentration in the buffer solution vs. time using an ultra violet (UV) light (234 nm) absorption measurement. The drug release (in PBS buffer) profile is shown in FIG. **8**.

Example 5

A membrane was fabricated as follows: A 35 wt % PLA polymer/DMF solution was prepared by slowly dissolving the PLA pellets. The solution was fed through the syringe pump system to the electrodes at a flow rate of 20 microliters/min per jet. A 25 kV positive high voltage was applied to the electrode. FIG. **9** shows a typical scanning electron microscopy (SEM) image of an electrospun PLA membrane made by the procedures described above. It has an average fiber diameter of 200 nm. The typical membrane density is about 0.25 g/cm^3, as compared to the neat resin (PLA) density of 1.3 g/cm^3.

Example 6

An in-vitro biodegradation test was conducted to evaluate the performance of electrospun membranes. The biodegradation test was conducted using the following method, which is routinely used in the suture industry: a PGA membrane was submerged in a buffer solution containing sodium phosphate, potassium phosphate, and distilled water (pH 7.3), and maintained at 37° C. The weight loss was measured as a function of time. The test was repeated for a PLA membrane. The results for both membranes are plotted in FIG. **10**. A review of FIG. **10** reveals that the major weight loss (50%) varies from 2 weeks (PGA) to about 6 months (PLA).

Example 7

A membrane containing dual thickness fibers was prepared as follows: a 25 wt % PLA-DMF solution was prepared by slowly dissolving PLA polymer pellets having the same molecular weight and poly dispersity as in Example 3 into a DMF solvent. A drug solution was prepared by dissolving 0.6 grams of Mefoxin (Merck & Co Inc.) into 0.4 grams of water. The drug solution was then very slowly (dropwise) added to the polymer solution with gentle stirring until it reached a final PLA/drug ratio of 19:1. A 20 kV positive high voltage (by Glassman High Voltage Inc.) was applied on the electrode. All other parameters were the same as Example 1. A membrane having a network structure consisting of large size filaments (2 micron diameter), very fine fibrils (50 nanometer diameter) and small blobs was obtained by varying the solution feed rate over a range from 20 μl/min to 70 μl/min. An SEM of the resulting membrane is shown in FIG. **11**.

The membrane was then placed in the buffer solution described in Example 6. After one week of degradation in the control buffer, the fine fibers completely disappeared

(FIG. 12). A comparison of FIGS. 11 and 12 reveals that this morphology results in a rapid weight loss in the first week. Thus, if more rapid weight loss is desired, a membrane having a higher concentration of thin fibrils can be produced.

Example 8

An experiment was conducted to evaluate the barrier properties of different membranes for preventing post-operative induced adhesions. The experiment used an objective rat model (ORM) to evaluate the performance of electrospun PLA-co-PGA membranes, with and without an antibiotic drug (Mefoxin) contained in the membrane structure, which were prepared in the same manner as in Examples 1 (without the drug) and 4 (with the drug). A control group was also used for comparison.

The test procedures used were as follows: the membrane being tested was first sterilized using ^{60}Co radiation source. The membrane sample was sealed in a plastic bag in a container filled with dried nitrogen gas. The package then received γ-radiation doses from 5.15~25 kGy, depending on the mass. This procedure has been well documented in the literature.

300–450 gram male Sprague-Dawley rats were used in the experiments. They were individually housed and given food and water ad libitum both pre- and postoperatively. Anesthesia was produced using an IM ketamine (80 mg/kg) and xylaxine (10 mg/kg) injection into the right hindleg prior to the celiotomy. Euthanasia was performed using intracardiac injection of pentobarbital (60 mg/kg).

The rats were divided into two procedure groups. The first group underwent a midline celiotomy and the cecum identified and scored using an abrasive pad until serosal bleeding was noted on the anterior surface. A1×1 cm square of abdominal wall muscle was then excised directly over the cecal wound. The first group experiment was conducted using 12 animals with the membrane and 14 animals with the membrane containing antibiotics, which were compared to 12 control animals (cecal abrasions and buttons without any membrane). The celiotomy was then closed in two layers immediately (control, n=12), after a barrier was laid in between the cecum and the abdominal wall (n=12), or after an antibiotic-impregnated barrier was placed in the aforementioned are (n=14). All rats underwent a second celiotomy after 4 weeks. The presence or absence of adhesions from the cecum to the abdominal wall was noted. The cecum was then isolated from the rest of the bowel and the breaking strength of the adhesion was measured by using a tensiometer.

In the first group of experiments, cecal adhesions were noted in 67% of the control set, 50% of the set with barriers, and 38% of the set with barriers impregnated with antibodies (see FIG. 13). Tensiometer readings on those adhesions present were found to be 6.18, 5.76, and 4.30 respectively (see FIG. 14). Only adhesions from the cecum to the abdominal wall were counted. Adhesional bands between the bowel and other abdominal organs were noted on occasion, but were not taken into account.

In the second group experiment, Marlex mesh, a material often used in abdominal surgery to repair the abdominal wall, was used to test the membranes. This mesh has the severe complication of causing adhesions to the intestines which not only leads to bowel obstruction, but also fistula formation. Both complications can be devastating to patients. The Marlex mesh was applied to a defect created in the abdominal wall and 10 animals had the barrier membrane interposed between the mesh and the intestines, while 10 controls had the Marlex placed with no interposing membrane. The second group of rats had Marlex mesh placed into the abdominal cavity. The abdomen was opened using a midline celiotomy and a 1×1 cm square of Marlex mesh was placed over the cecum and fixed to the abdominal wall using two silk sutures. The abdomens were then either immediately closed in two layers (control, n=10) or had a barrier placed in between the cecum and the mesh (n=10). All animals underwent a second celiotomy after 4 weeks. The presence or absence of adhesions between the cecum and mesh were noted.

In the group of rats with Marlex mesh, the first set of rats all has adhesions from the cecum to the mesh (100%). The mesh also has a multitude of other adhesions to the omentum, stomach, and liver making a measurement of adhesional strength from cecum to abdominal wall problematic. The set with barriers was found to have only one rat with adhesions from the cecum to the abdominal wall (10%).

Overall, the test results showed good barrier properties of the membranes, i.e., a low incidence of induced adhesion in the membrane embedded area, while an adhesion was induced in the control area. The membrane containing the antibiotic showed better barrier properties than the membrane without the antibiotic.

Example 9

The antibacterial effect of drug containing membranes was tested using the following procedures: 8 ml of Luria Broth (LB) and 80 microliters of *E. coli* cells were added to each of four sample test tubes. A 7.0×7.0 cm sample of a PLA electrospun membrane having a thickness of about 75 microns (with a corresponding total weight of 100 mg) was added to one of the test tubes. A second sample of a PLA membrane containing approximately 4.83 mg of Mefoxin was added to another test tube. A third sample of a PLA membrane containing approximately 8.85 mg of Mefoxin was added to a third test tube. The last test tube was used as a control.

LB was used to grow the *E. coli* bacterial cells. The sample tubes were placed in an incubator overnight. The temperature of the incubator was set at 37° C. and the shaking rate was set at 225 rpm. Shaking was necessary in order for the *E. coli* bacteria to receive enough nutrients needed to grow. Using a SmartSpec *3000 instrument, the optical density (OD) at the 600 nm wavelength for *E. coli* bacteria was recorded and the amount of cells in each test tube was calculated. The cell concentration could be related to the product of the optical density of each sample and a conversion factor. As the optical density increases (the broth becomes more turbid), the cell concentration should increase. The results are shown in FIG. 15, with the y-axis unit being cell/ml or the bacteria concentration.

A review of FIG. 15 reveals that the growth of *E. coli* bacteria is completely prohibited by the release of the Mefoxin antibiotic drug from the membrane containing 8.85 mg of the drug. Also, it appears that the higher the loading concentration of Mefoxin, the more effective the membrane becomes.

Example 10

An in-vivo biodegradation test was conduced using a PLA electrospun membrane having an average fiber diameter in the range of about 100–150 nanometers. The membrane was fabricated as follows. A 25 wt % PLA solution in DMF was prepared. A 60 wt % Mefoxin drug in aqueous solution was then added to the polymer solution to reach a final PLA/drug

ration of 9:1. A 20 kV positive voltage was applied to the electrode. An SEM of the initial as spun membrane (FIG. **16**) shows smooth fibrous structures with an average fiber diameter between 100–150 nm. The membrane was implanted into a rat and removed after one week, following the procedures described in Example 8. An SEM of the partially biodegraded membrane is shown in FIG. **17**.

A comparison of FIGS. **16** and **17** reveals that the morphology of the membrane has been changed, resulting in a more porous structure.

Example 11

A bioabsorbable composite membrane consisting of two polymer components of different hydrophobicity according to the present invention was prepared as follows: First, a 6 wt % polyethylene oxide (PEO)/DMF solution was prepared by slowly adding the polymer powders into an organic solvent, which was DMF (N,N-dimethyl formamide). Second, a 30 wt % polylactide glycolide (PLG)/DMF solution was made by dissolving the polymers into DMF as well. After these two solutions were each completely homogenized at the room temperature, they were then loaded separately into two individual syringes, each with a volume of 5 mL. Next, the syringes were fitted with 2 gauge 20 needles and delivered through Teflon tubes to the electrodes, each having a tiny hole with a diameter of 0.025". The polymer solutions were finally pumped and controlled by a syringe pump at a flow rate of 20 microliters/min. In addition, a 25 kV positive high voltage was applied on two separate electrodes in order to obtain the existence of well-stabilized electrospinning jets. The distance from the tips of the electrodes to the ground collecting plate was 15 cm. Furthermore, a step motor was utilized in order to control the movement of the ground collector so that it was capable to move in different directions, either left or right. The collecting plate was moving at a rate of 5 steps/sec continuously until a bioabsorable membrane having a relatively uniform thickness of 100 microns was achieved.

Example 12

A bioabsorbable composite membrane consisting of two component polymer blend of different hydrophobicity according to the present invention was prepared as follows: First, a 2 wt % polyethylene oxide (PEO, Mw=100,000 g/mol)/DMF solution was prepared by slowly adding the polymer powders into an organic solvent, which was DMF (N,N-dimethyl formamide). Second, a 20 wt % polylactide glycolide (PLG)/DMF solution was made by dissolving the polymers into DMF as well. These two solutions were mixed together and were each completely homogenized at the room temperature. They were then loaded separately into two individual syringes, each with a volume of 5 mL. Next, the syringes were fitted with 2 gauge 20 needles and delivered through Teflon tubes to the electrodes, each having a tiny hole with a diameter of 0.025". The polymer solutions were finally pumped and controlled by a syringe pump at a flow rate of 20 microliters/min. In addition, a 25 Kv positive high voltage was applied on two separate electrodes in order to obtain the existence of well-stabilized electrospinning jets. The distance from the tips of the electrodes to the ground collecting plate was 15 cm. Furthermore, a step motor was utilized in order to control the movement of the ground collector so that it was capable to move in different directions, either left or right. The collecting plate was moving at a rate of 5 steps/sec continuously until a bioabsorable membrane having a relatively uniform thickness of 100 microns was achieved.

Thus, while there has been disclosed what is presently believed to be preferred embodiments of the invention, those skilled in the art will appreciate that other and further changes and modifications can be made without departing from the scope or spirit of the invention, and it is intended that all such other changes and modifications are included in and are within the scope of the invention as described in the appended claims.

We claim:

1. A system for controlled delivery of a medicinal agent comprising a medicinal agent to be delivered and a biodegradable and/or bioabsorbable fibrous article physically associated with said medicinal agent to release said agent at a controlled rate, said fibrous article comprising a composite of different biodegradable and/or bioabsorbable fibers or an asymmetric composite of different biodegradable and/or bioabsorbable fibers.

2. A system according to claim **1**, wherein different fibers refers to fibers of different diameters.

3. A system according to claim **2**, wherein said fibers of different diameters include fibers having diameters less than 1 micron and fibers having diameters greater than 1 micron.

4. A system according to claim **3**, wherein said fibrous article comprises at least about 20 weight percent of submicron diameter fibers.

5. A system according to claim **4**, wherein said fibrous article comprises at least about 50 weight percent of submicron diameter fibers.

6. A system according to claim **1**, wherein different fibers refers to fibers of different biodegradable and/or bioabsorbable materials.

7. A system according to claim **1**, wherein different fibers refers to fibers of different diameters and different biodegradable and/or bioabsorbable materials.

8. A system according to claim **1**, wherein said biodegradable and/or bioabsorbable fiberizable material comprises a biodegradable and/or bioabsorbable polymer.

9. A system according to claim **8**, wherein said biodegradable and/or bioabsorbable polymer comprises a monomer selected from the group consisting of a glycolide, lactide, dioxanone, caprolactone, trimethylene carbonate, ethylene glycol and lysine.

10. A system according to claim **8**, wherein said biodegradable and/or bioabsorbable polymer comprises a biodegradable and/or bioabsorbable linear aliphatic polyester.

11. A system according to claim **10**, wherein said biodegradable and/or bioabsorbable linear aliphatic polyester is a polyglycolide or a copolymer poly(glycolide-co-lactide).

12. A system according to claim **1**, wherein said biodegradable and/or bioabsorbable fiberizable material comprises a material derived from biological tissue.

13. A system according to claim **1**, wherein said fibers have diameters in the range from about 10 up to 1,000 nanometers.

14. A system according to claim **13**, wherein said fibers have diameters in the range from about 20 to about 500 nanometers.

15. A system according to claim **1**, further comprising small blobs of biodegradable and/or bioabsorbable material.

16. A system according to claim **1**, further comprising at least one medicinal agent.

17. A system according to claim **16**, wherein said medicinal agent is contained within said fibers.

18. A system according to claim **17**, further comprising fibers with different concentrations of said medicinal agent.

19. A system according to claim **17**, further comprising fibers with different medicinal agents.

20. A system according to claim 1, further comprising a plurality of layers, wherein at least one of the layers comprises a composite or asymmetric composite of different biodegradable and/or bioabsorbable fibers.

21. A system according to claim 20, further comprising at least one medicinal agent between at least two of said layers.

22. A system according to claim 1, wherein said fibrous article has a controlled degradation rate.

23. A system according to claim 1, wherein said fibrous article is a membrane.

24. A system according to claim 23, wherein said membrane has a thickness in the range of about 10 to about 5000 microns.

25. A system according to claim 24, wherein said membrane has a thickness in the range of about 20 to about 1000 microns.

26. A method for controlled delivery of a medicinal agent which comprises implanting at a target site in an animal, a system for controlled delivery of a medicinal agent, said system comprising a medicinal agent to be delivered and a biodegradable and/or bioabsorbable fibrous article physically associated with said medicinal agent to release said agent at a controlled rate, wherein said article comprises a composite of different biodegradable and/or bioabsorbable fibers or an asymmetric composite of different biodegradable and/or bioabsorbable fibers.

27. A method according to claim 26, wherein different fibers refers to fibers of different diameters.

28. A method according to claim 26, wherein different fibers refers to fibers of different biodegradable and/or bioabsorbable materials.

29. A method according to claim 26, wherein different fibers refers to fibers of different diameters and different biodegradable and/or bioabsorbable materials.

* * * * *

US007172765B2

(12) **United States Patent**
Chu et al.

(10) **Patent No.: US 7,172,765 B2**
(45) **Date of Patent: Feb. 6, 2007**

(54) **BIODEGRADABLE AND/OR BIOABSORBABLE FIBROUS ARTICLES AND METHODS FOR USING THE ARTICLES FOR MEDICAL APPLICATIONS**

(75) Inventors: **Benjamin Chu**, Setauket, NY (US); **Benjamin S. Hsiao**, Setauket, NY (US); **Dufei Fang**, Painted Post, NY (US); **Collin Brathwaite**, Setauket, NY (US)

(73) Assignee: **The Research Foundation of State University of New York**, Stony Brook, NY (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 411 days.

(21) Appl. No.: **10/719,290**

(22) Filed: **Nov. 21, 2003**

(65) **Prior Publication Data**

US 2004/0076661 A1 Apr. 22, 2004

Related U.S. Application Data

(62) Division of application No. 10/375,329, filed on Feb. 27, 2003, now Pat. No. 6,689,374, and a division of application No. 09/859,007, filed on May 16, 2001, now Pat. No. 6,685,956.

(51) **Int. Cl.**
A61F 2/02 (2006.01)

(52) **U.S. Cl.** **424/423**; 424/424; 424/425; 424/426

(58) **Field of Classification Search** 424/423, 424/424, 425, 426
See application file for complete search history.

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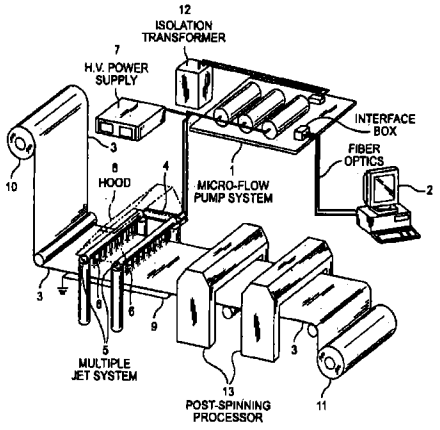
Primary Examiner—Carlos A. Azpuru
(74) *Attorney, Agent, or Firm*—Hoffmann & Baron, LLP

(57) **ABSTRACT**

Biodegradable and/or bioabsorable fibrous articles and methods for using the articles in medical applications are disclosed. The biodegradable and/or bioabsorable fibrous articles, which are formed by elctrospinning fibers of biodegradable and/or bioabsorbable fiberizable material, comprise a composite (or asymmetric composite) of different biodegradable and/or bioabsorbable fibers. Articles having specific medical uses include an adhesion-reducing barrier and a controlled delivery system. The methods include methods for reducing surgical adhesions, controlled delivery of a medicinal agent and providing controlled tissue healing.

60 Claims, 14 Drawing Sheets



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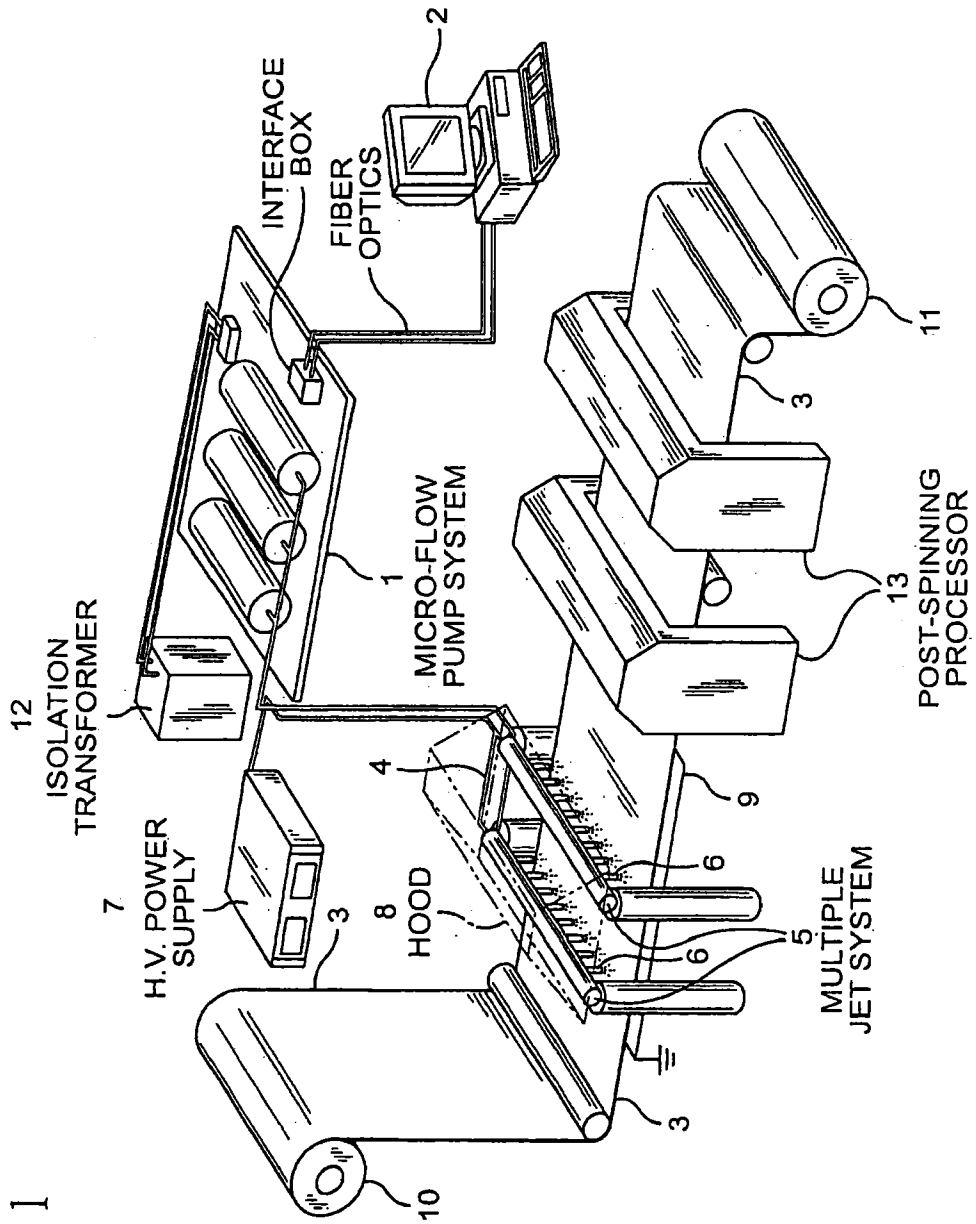

12
ISOLATION TRANSFORMER
7
H.V. POWER SUPPLY
INTERFACE BOX
FIBER OPTICS
2
1
MICRO-FLOW PUMP SYSTEM
4
8
HOOD
3
6
5
MULTIPLE JET SYSTEM
9
13
POST-SPINNING PROCESSOR
11
10

FIG. 1

FIG. 2 (a)

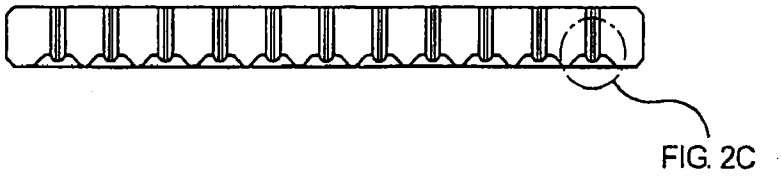


FIG. 2 (b)

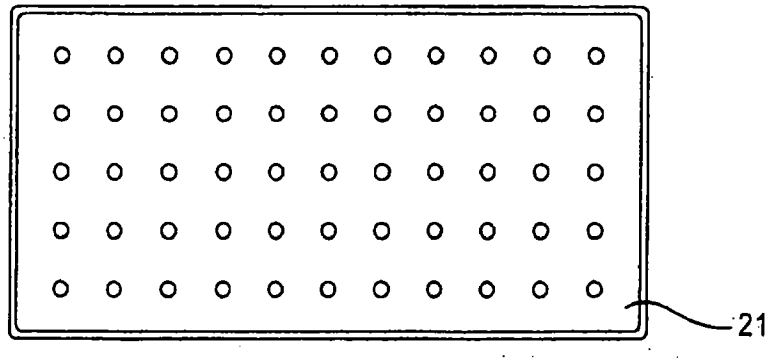


FIG. 2 (c)

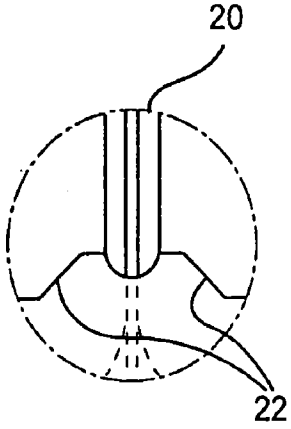


FIG. 3 (a)

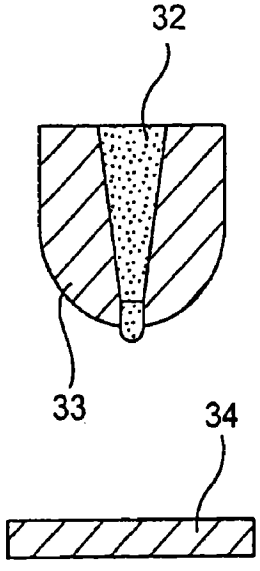


FIG. 3 (b)

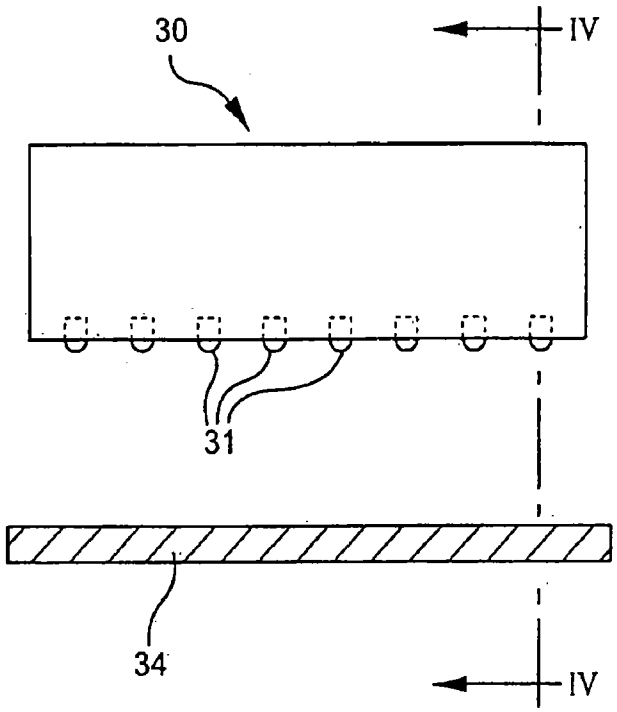


FIG. 3 (c)

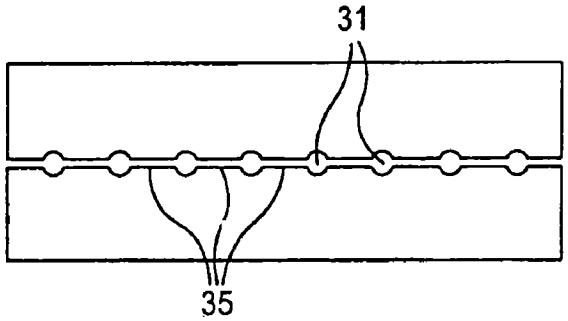


FIG. 4 SPUN MEMBRANE WITH 1 WT% KH_2PO_4

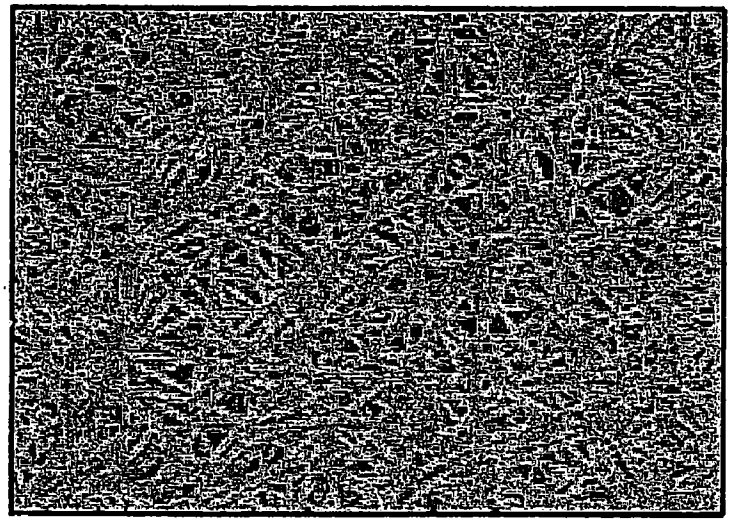
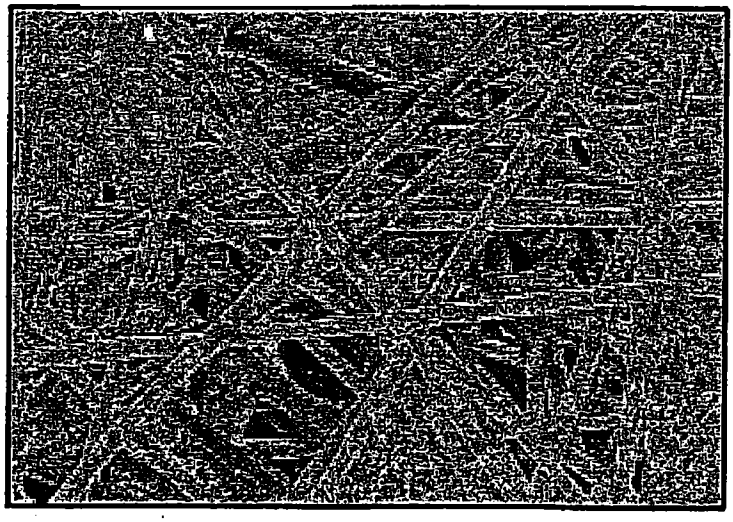


FIG. 5 SPUN MEMBRANE WITHOUT SALT



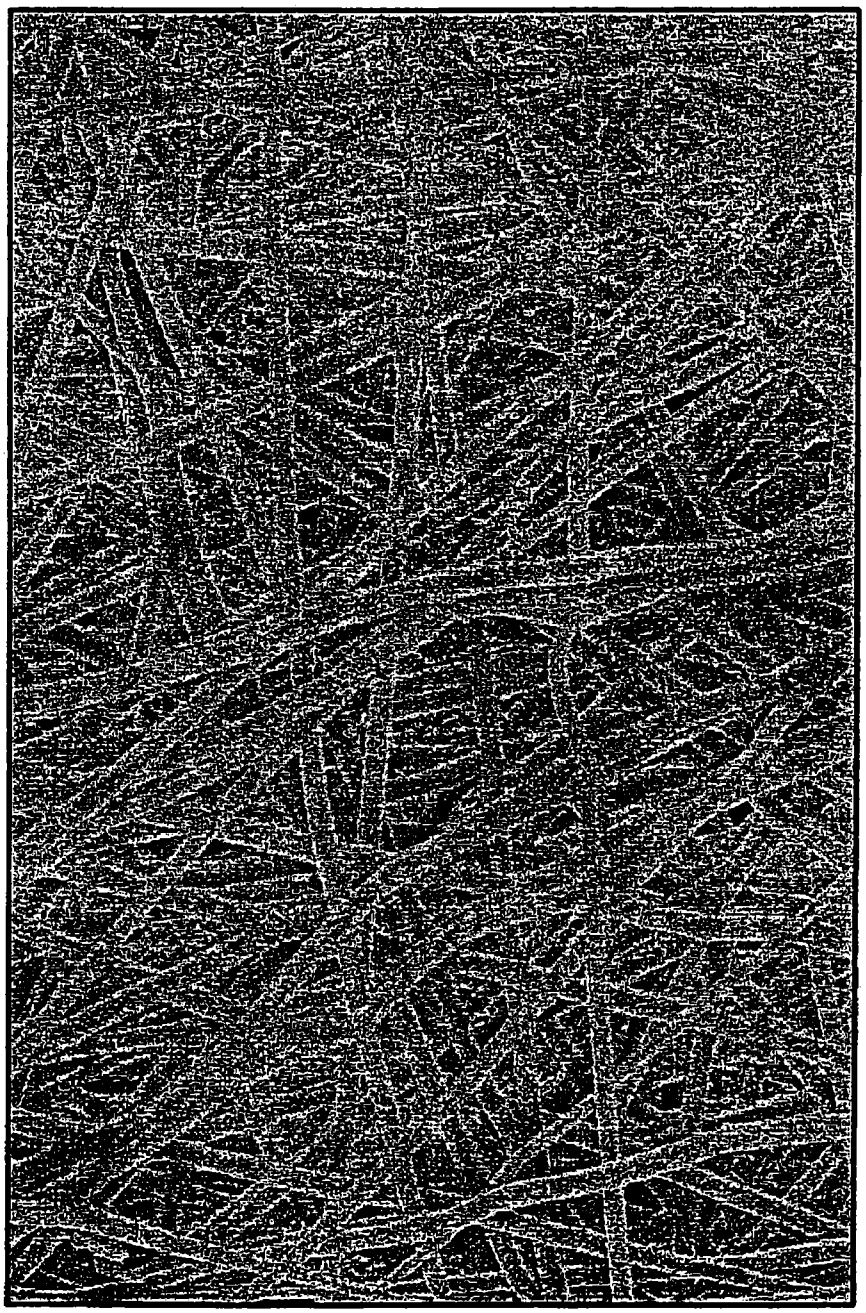


FIG. 6

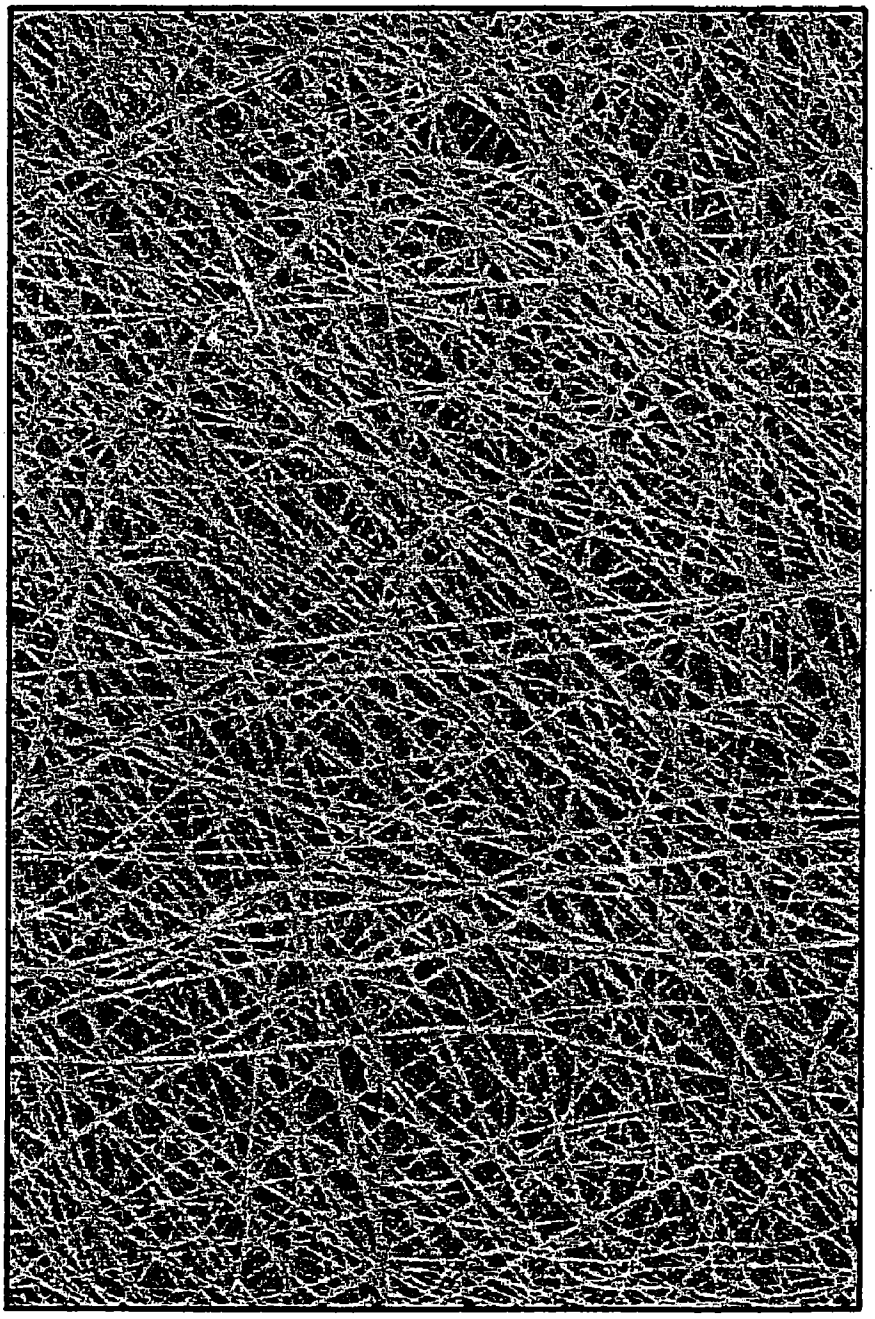


FIG. 7

FIG. 8 IN VITRO DRUG RELEASE PROFILE

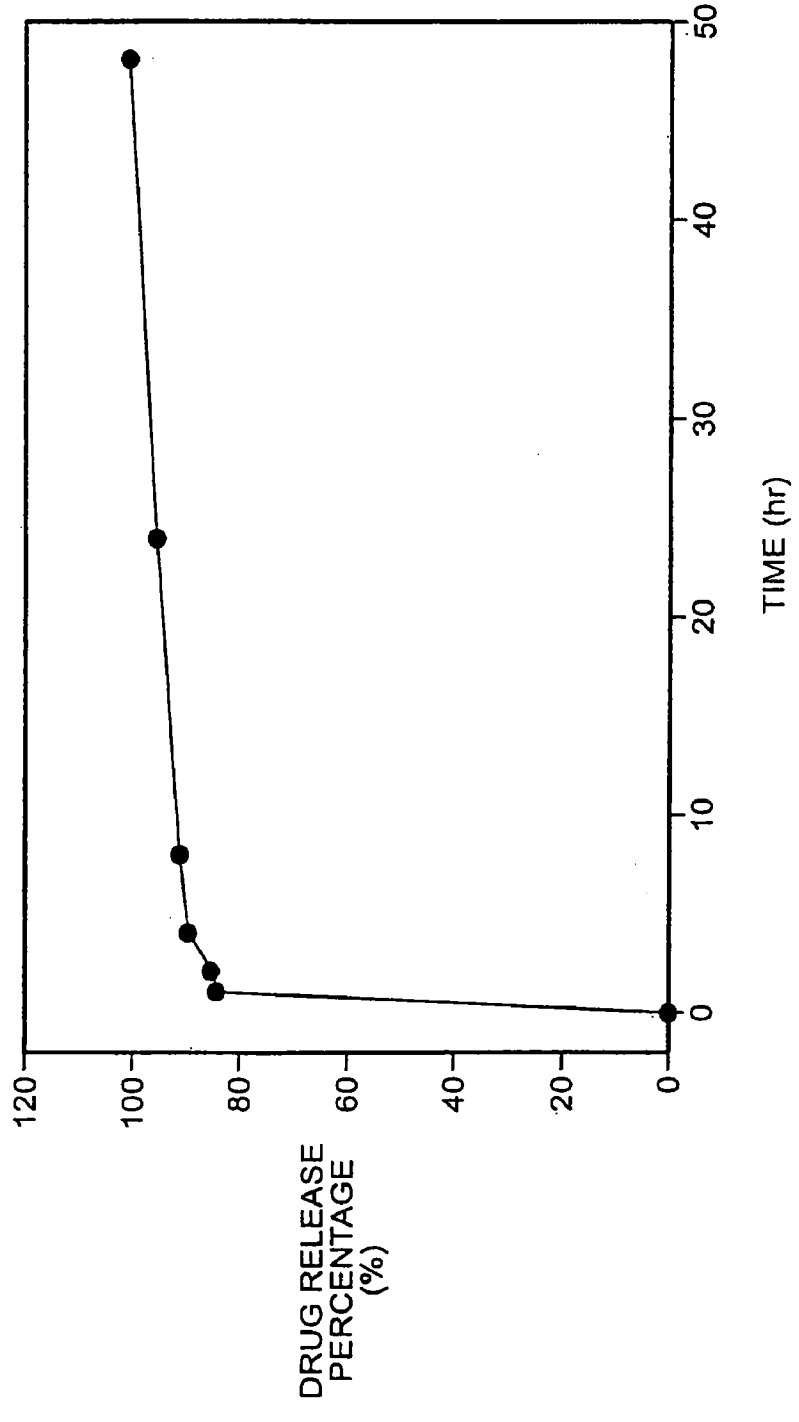


FIG. 9 SEM IMAGE OF ELECTROSPUN PLA MEMBRANE

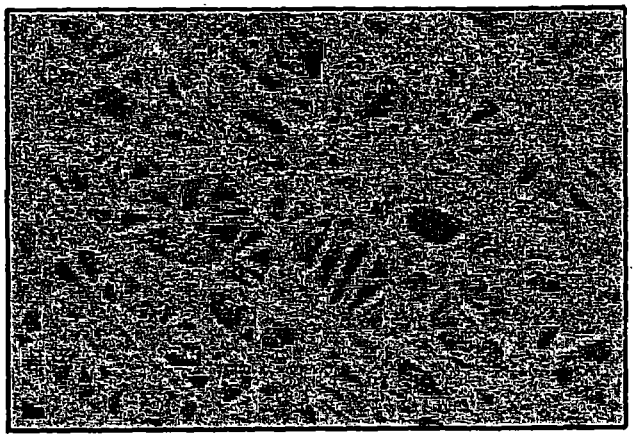


FIG. 10 BIODEGRADATION RATE OF ELECTROSPUN MEMBRANE

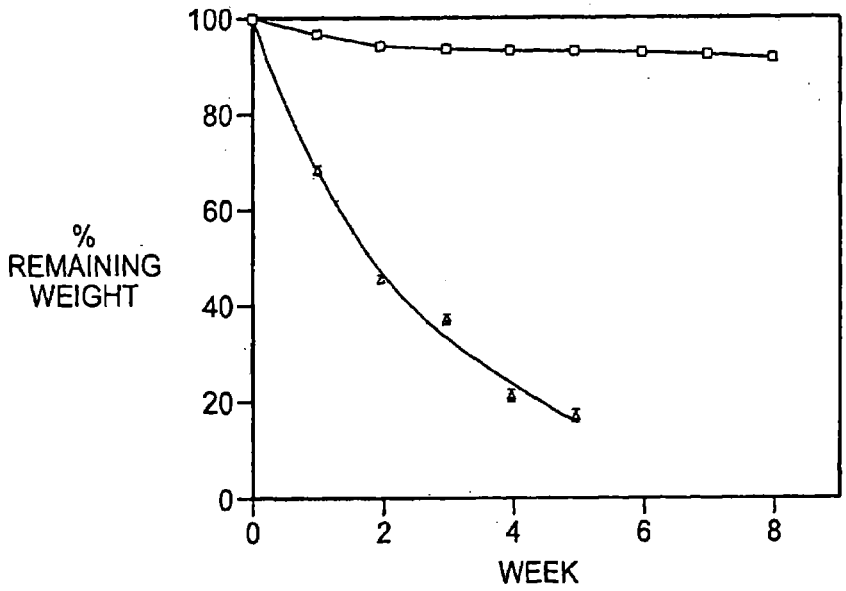


FIG. 11 DUEL THICKNESS PLA MEMBRANE

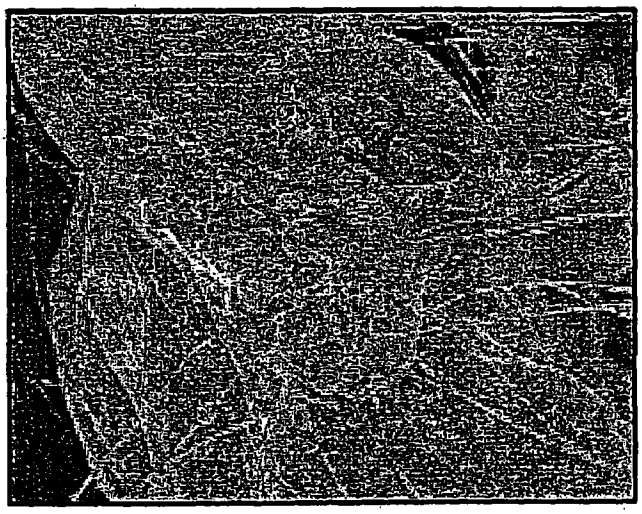


FIG. 12 MEMBRANE AFTER 1 WEEK OF DEGRADATION

FIG. 13 INCIDENCE OF ADHESION

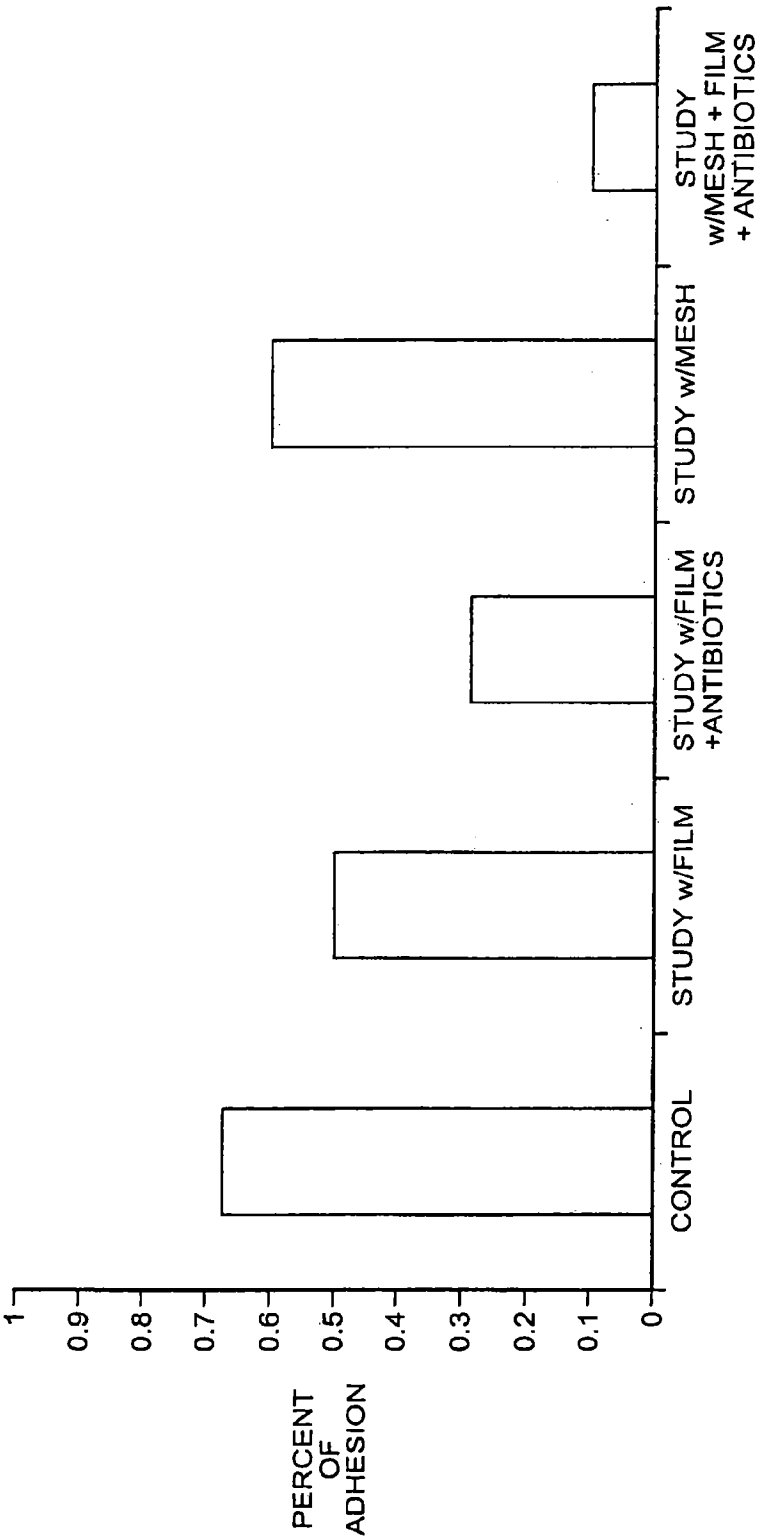


FIG. 14 CECAL ADHESION TENSION (N)

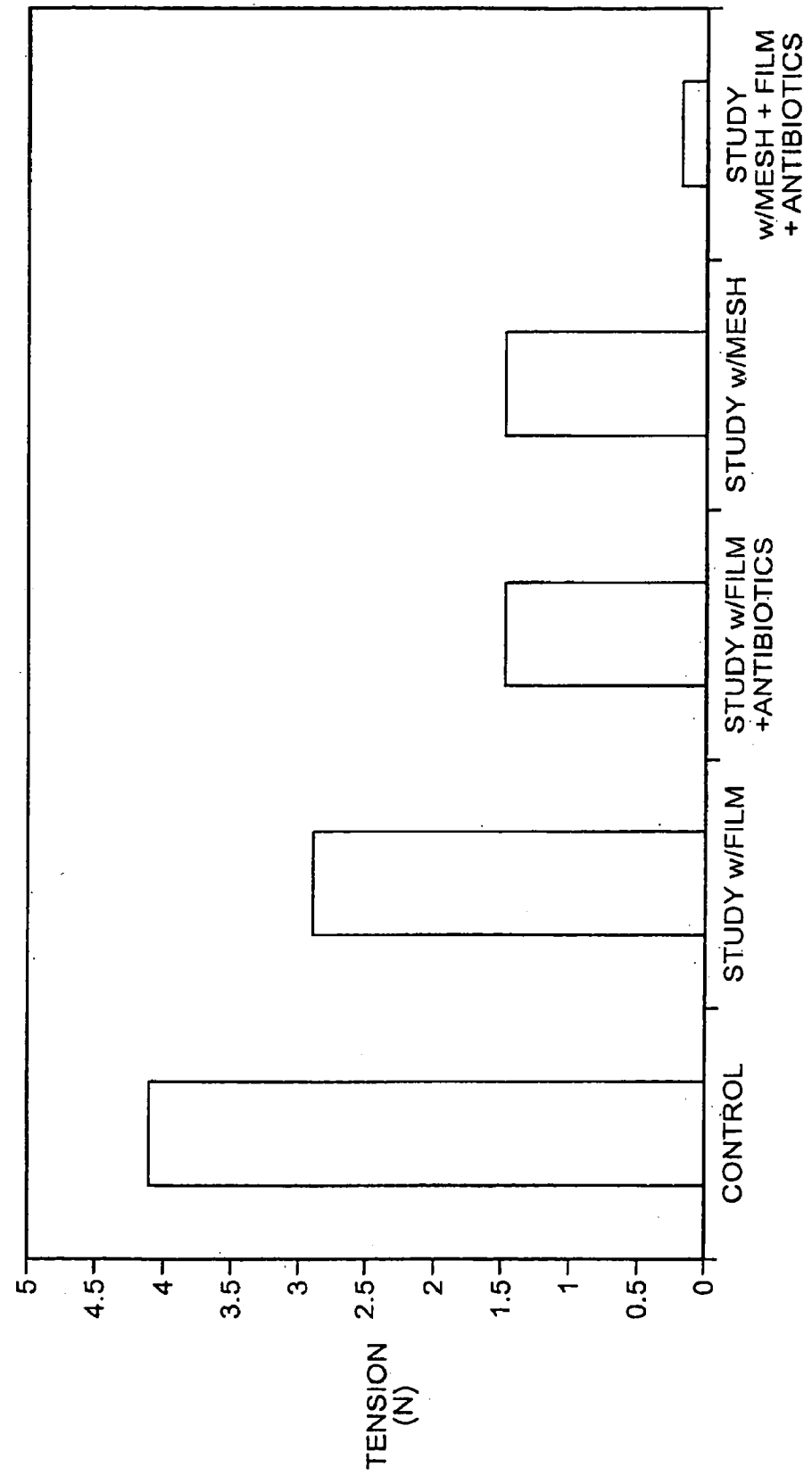


FIG. 15 ANTIBACTERIAL TEST RESULTS OF PLA MEMBRANE

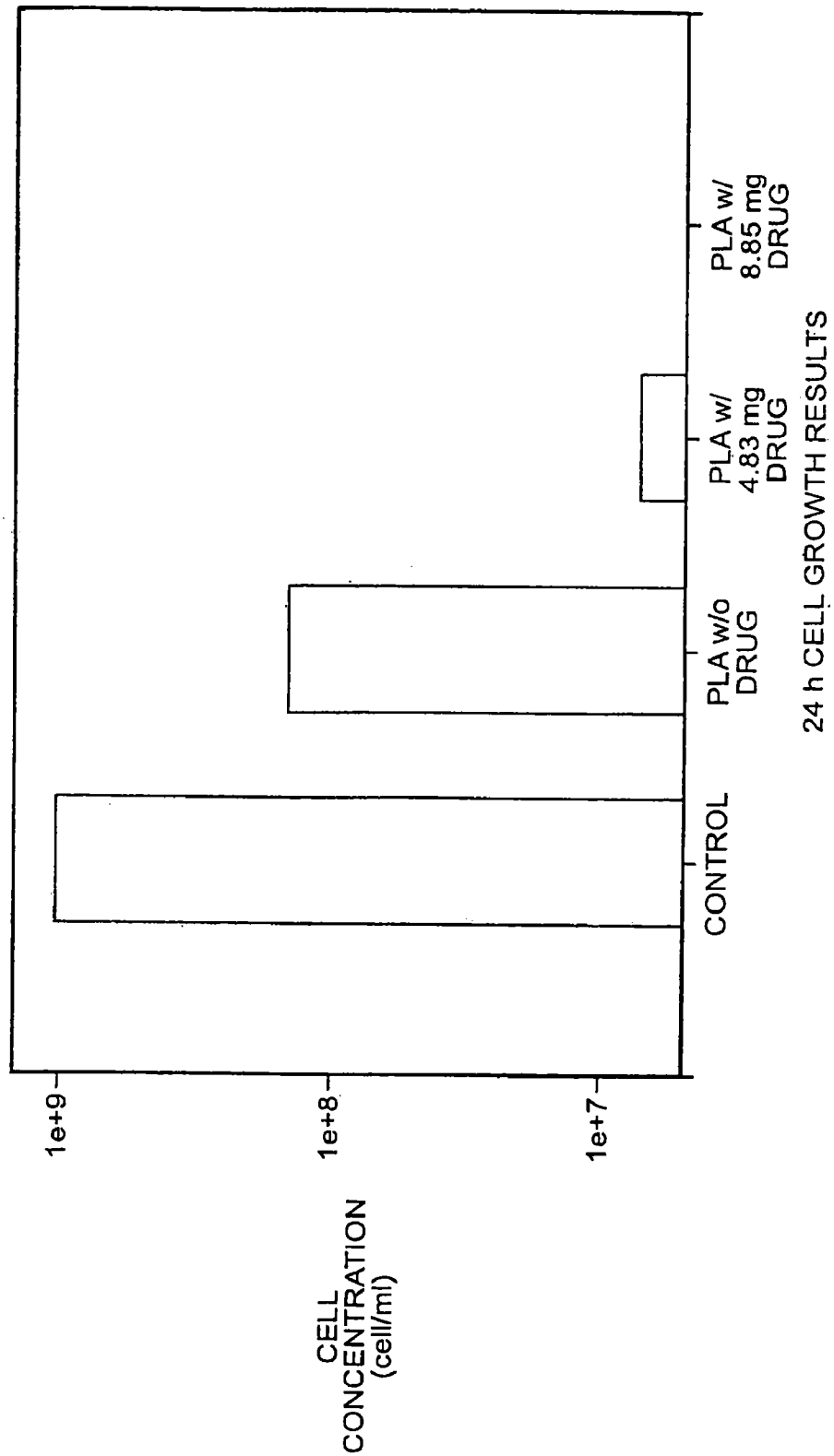


FIG. 16 SEM IMAGE OF AS-SPUN MEMBRANE

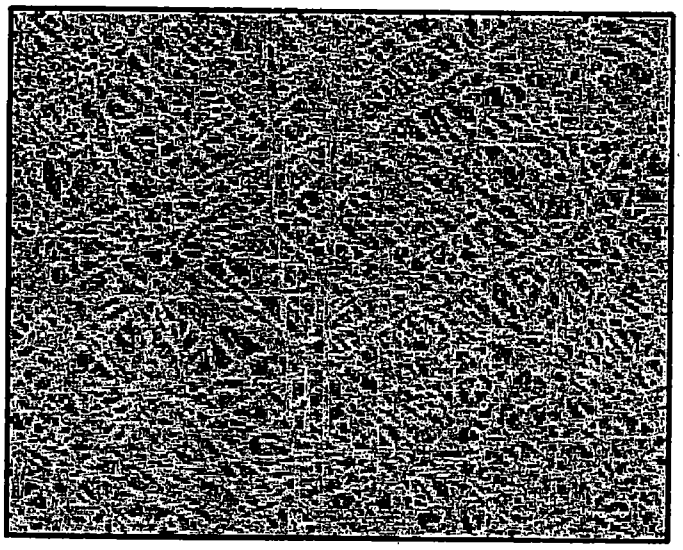
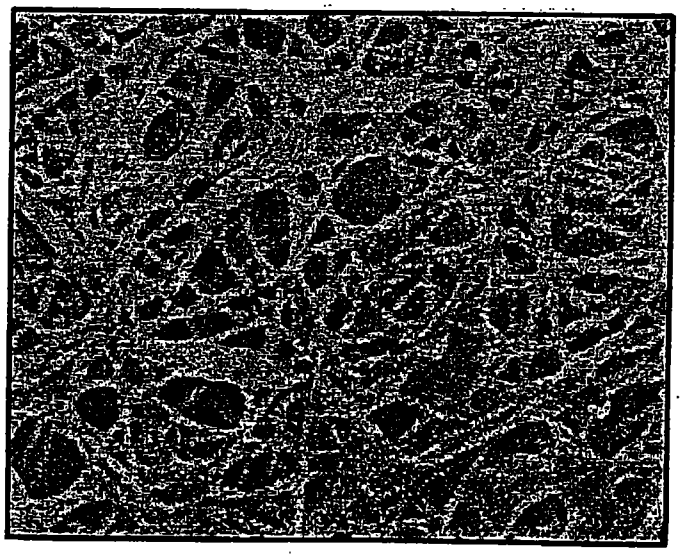


FIG. 17 *IN-VIVO* DEGRADATION AFTER A WEEK



BIODEGRADABLE AND/OR BIOABSORBABLE FIBROUS ARTICLES AND METHODS FOR USING THE ARTICLES FOR MEDICAL APPLICATIONS

This application is a divisional of application Ser. No. 10/375,329, filed on Feb. 27, 2003 now U.S. Pat. No. 6,689,374 Ser. No. 09/859,007 filed on May 16, 2001.

BACKGROUND OF INVENTION

The present invention relates to biodegradable and/or bioabsorbable fibrous articles. More specifically, the present invention is directed to products and methods having utility in medical applications. In one embodiment, the fibrous articles of the invention are polymeric membranes.

Polymeric membranes produced by an electrospinning technique have been suggested as being useful for biological membranes such as substrates for immobilized enzymes and catalyst systems, wound dressing materials and artificial blood vessels, as well as for aerosol filters and ballistic garments.

Electrospinning is an atomization process of a conducting fluid which exploits the interactions between an electrostatic field and the conducting fluid. When an external electrostatic field is applied to a conducting fluid (e.g., a semi-dilute polymer solution or a polymer melt), a suspended conical droplet is formed, whereby the surface tension of the droplet is in equilibrium with the electric field. Electrostatic atomization occurs when the electrostatic field is strong enough to overcome the surface tension of the liquid. The liquid droplet then becomes unstable and a tiny jet is ejected from the surface of the droplet. As it reaches a grounded target, the material can be collected as an interconnected web containing relatively fine, i.e. small diameter, fibers. The resulting films (or membranes) from these small diameter fibers have very large surface area to volume ratios and small pore sizes. However, no practical industrial process has been implemented for producing membranes useful for medical applications. This is because with the production of small fibers, such as nanosize fibers, the total yield of the process is very low and a scale-up process, which maintains the performance characteristics of the films (or membranes), cannot be easily achieved.

U.S. Pat. No. 4,323,525 is directed to a process for the production of tubular products by electrostatically spinning a liquid containing a fiber-forming material. The process involves introducing the liquid into an electric field through a nozzle, under conditions to produce fibers of the fiber-forming material, which tend to be drawn to a charged collector, and collecting the fibers on a charged tubular collector which rotates about its longitudinal axis, to form the fiberous tubular product. It is also disclosed that several nozzles can be used to increase the rate of fiber production. However, there is no suggestion or teaching of how to control the physical characteristics of the tubular product, other than by controlling the charge and rotation speed of the tubular collector. It is further noted that the spinning process of the '525 patent is used to fabricate tubular products having a homogenous fiber matrix across the wall thickness.

U.S. Pat. No. 4,689,186 is directed to a process for the production of polyurethane tubular products by electrostatically spinning a fiber-forming liquid containing the polyurethane. It is disclosed that auxiliary electrodes can be placed around the collector to help facilitate collection of the fibers. It is disclosed that the auxiliary electrodes can be arranged to facilitate separation or to prevent adhesion of the formed fibers. There is no teaching or suggestion of independently controlling jet formation, jet acceleration and fiber collection. It is also noted that the spinning process of the '186 patent is used to fabricate tubular products having a homogenous fiber matrix across the wall thickness.

In one aspect, the present invention is directed to products and methods for preventing the formation of post-surgical adhesions between a healing trauma site and adjacent surrounding tissue.

Adhesion formation is a natural and inevitable consequence of surgery. Injury, surgical incisions, abrasion or other operative damage to the peritoneum, pleural or abdominal cavity results in an outpouring of a serosanguinous exudate. This exudate can accumulate on the injured surface and subsequently coagulate, producing fibrinous bands between abutting surfaces which can become organized by fibroblast proliferation to become collagenous adhesions. Adhesions are also known to form at bone fracture sites resulting in adhesions between the bone fracture surface and the surrounding tissue.

Adhesions can lead to serious complications. For example, adhesions that form in relation to intestinal surgery such as bowel resection, hernia repair, etc., may cause obstruction of the intestine. Adhesions that form near a bone fracture site may reduce or hinder the normal movement of the area of repair by restricting the natural movement of tendons over the adjacent bone. Adhesions may also form in the vicinity of nerves and disrupt nerve transmissions with a resultant diminution of sensory or motor function. Adhesions have also been known to lead to female infertility, chronic debilitating pain and difficulty with future operations. Typically, a patient will often have to undergo additional surgery to remove adhesions, only to have them reform.

Various methods and substances have been used in the hope of preventing post-operative adhesions. Certain drugs and surfactants have been suggested. For example, U.S. Pat. No. 4,911,926 is directed to adhesion prevention by application of aqueous and non-aqueous compositions of a polyoxyalkylene block copolymer to injured areas of the peritoneal or pleural cavity or organs situated therein subsequent to surgical injury.

Other surgical adjuvants have been used in an attempt to minimize or prevent adhesions following surgery, including anti-inflammatory drugs (such as corticosteroids) to decrease vascular permeability, antihistamines to reduce fibroblast proliferation, anticoagulants (such as heparin) and antibiotics (such as vibramycin or metokin) to reduce the incidence of infection. However, the use of drugs or compositions which are applied to the surgical area have only had limited success in preventing adhesions.

Another approach to adhesion prevention involves application of a physical barrier at the area of surgical injury. The theory is that a mechanical barrier, placed between the injured, healing serosal surfaces, which persists until all serosal healing has taken place will prevent adhesions and the sequela, e.g., small bowel obstruction. Bioabsorbable materials in the form of barrier layers to prevent adhesions of tissues which have been suggested include products based on cellulose materials. However, the use of commercial cellulose based products to prevent adhesions has certain drawbacks. For example, the performance in preventing adhesions is limited. Furthermore, certain products have been reported to have handling problems during surgery or can cause scars after use.

U.S. Pat. No. 4,674,488 is directed to interposing a barrier layer of soft biological tissue, such as collagen, collagen-

fabric films, collagen membranes, or reconstituted collagen or Dacron™, mesh, at the interface of a bone fracture and the surrounding tissue. U.S. Pat. No. 4,603,695 is directed to a molded polymeric material for preventing adhesion of vital tissues. The polymeric material is made of a biodegradable and absorbable polymer such as certain polyesters, collagen, amino acid polymers and chitin and may be placed where there is a possibility of adhesion setting in. Although biological materials, such as collagen, are generally "biocompatible," they can generate scars when implanted in certain forms, and it is difficult to precisely control the degradation of such materials.

Other materials have also been used to form physical barriers in an attempt to prevent adhesions, including silicone elastomers, gelatin films and knit fabrics of oxidized regenerated cellulose (hereinafter ORC). In some cases, it is suggested that heparin, heparinoid, or hexuronyl hexosaminogly can be incorporated into the matrix of an ORC fabric or other matrices of hyaluronic acid, cross-linked and uncross-linked collagen webs, synthetic resorbable polymers, gelatin films, absorbable gel films, oxidized cellulose fabrics and films which are fabricated into a form that is said to be drapable, conformable and adherent to body organs and substantially absorbable within 30 days. See, e.g., U.S. Pat. No. 4,840,626 or EPA Publication No. 0 262 890 or EPA Publication No. 0 372 969. However, as discussed above, it is difficult to precisely control the degradation rate of many of these materials and scar tissue can result from use of many of the materials.

Physical barriers are also used to cover and protect wound sites. PCT/US91/08972 is directed to a surgical article having a bioabsorbable fibrous matrix in a laminar relationship with a bioabsorbable cell barrier sheet. U.S. Pat. No. 5,092,884 and EPA Publication No. 0 334 046 are directed to a surgical composite structure having absorbable and non-absorbable components which may be useful for repairing anatomical defects, e.g., preventing hernia formation in an infected area. The nonabsorbable portion of the composite acts as a reinforcement material. The growth of natural tissue is said to be enhanced by controlled degradation of the absorbable portion. U.S. Pat. No. 5,035,893 relates to a wound covering composition having a sheet of biopolymeric material and a film of polyurethane resin. An antibacterial agent may be provided between the polyurethane film and the sheet of biopolymeric material, thereby forming a three-layer wound covering material. With the cure of the wound, it is said that the biopolymeric material is taken in as living tissue and the polyurethane film can be peeled off from the sheet without hurting the surface of a wound. Again, the use of many biopolymeric materials can result in the formation of scar tissue.

Thus, there is a need for improved membranes and other fibrous articles, which can be produced on an industrial scale, and for improved products and methods for reducing the formation of post-surgical adhesions, as well as for other medical applications, which do not have the above-mentioned disadvantages.

SUMMARY OF INVENTION

According to the present invention, it has now been found that biodegradable and/or bioabsorbable articles, e.g. membranes, having improved performance and handling characteristics for medical applications can be provided without the above-mentioned disadvantages.

In one aspect, the invention relates to a biodegradable and/or bioabsorbable fibrous article formed by electrospinning fibers of biodegradable and/or bioabsorbable fiberizable material, in which the article contains a composite of different biodegradable and/or bioabsorbable fibers.

In another aspect, the invention relates to a biodegradable and/or bioabsorbable fibrous article formed by electrospinning fibers of biodegradable and/or bioabsorbable fiberizable material, in which the article contains an asymmetric composite of different biodegradable and/or bioabsorbable fibers.

Different fibers can include fibers of different diameters, fibers of different biodegradable and/or bioabsorbable materials, or fibers of both different diameters and different biodegradable and/or bioabsorbable materials.

Preferably, the article will contain at least about 20 weight percent of submicron diameter fibers, more preferably, the article will contain at least about 50 weight percent of submicron diameter fibers.

Preferably, the biodegradable and/or bioabsorbable fiberizable material is a biodegradable and/or bioabsorbable polymer. The biodegradable and/or bioabsorbable polymer preferably contains a monomer selected from the group consisting of a glycolide, lactide, dioxanone, caprolactone, trimethylene carbonate, ethylene glycol and lysine.

In one embodiment the biodegradable and/or bioabsorbable polymer contains a biodegradable and/or bioabsorbable linear aliphatic polyester, more preferably a polyglycolide or a poly(glycolide-co-lactide) copolymer.

In another embodiment the biodegradable and/or bioabsorbable fiberizable material contains a material derived from biological tissue, e.g., collagen, gelatin, polypeptides, proteins, hyaluronan acid and derivatives or synthetic biopolymers.

The fibers of different biodegradable and/or bioabsorbable materials can include fibers having different chemical composition, such as different polymeric materials, different molecular weights of the same polymeric material, different blends of polymers, materials having different additives or materials having different concentration of additives.

In another embodiment the article will contain different fibers, i.e. different diameters and/or different materials, having diameters in the range from a few nanometers up to almost about one micron, more preferably about 10 up to about 1000 nanometers and most preferably from about 20 to about 500 nanometers. The fibers of different diameters can include both fibers having diameters less than 300 nanometers and fibers having diameters greater than 300 nanometers.

The article can also contain small blobs of biodegradable and/or bioabsorbable material. Preferably, the small blobs will have diameters in the range of about 20 to about 500 nanometers and, more preferably, about 200 to about 1500 nanometers.

In one embodiment, the article also contains at least one medicinal agent. The medicinal agent can be contained within the biodegradable and/or bioabsorbable material itself, including within the fibers or within the small blobs of material, if present. In such a case, the fibers (and/or small blobs) can contain different concentrations of the medicinal agent or different medicinal agents.

The article can also have the structure of a plurality of layers, wherein at least one of the layers is a composite (or asymmetric composite) of different biodegradable and/or bioabsorbable fibers. In such a case, the article can also contain at least one medicinal agent between at least two of the layers.

In one embodiment, the above described fibrous articles are in the form of a membrane.

The membrane according to the invention will preferably have a thickness in the range of about 10 to about 5000 microns, more preferably about 20 to about 1000 microns.

In another aspect, the invention relates to a fibrous article formed by electrospinning different fibers of different materials, in which the article contains a composite of different fibers containing fibers of at least one biodegradable material and fibers of at least one non-biodegradable material. Preferably, the compositite of different fibers will contain submicron diameter fibers. The composite can be an asymmetric composite.

In another aspect, the invention is directed towards an adhesion-reducing barrier containing a biodegradable and/or bioabsorbable membrane, in which the membrane contains:

a composite of different biodegradable and/or bioabsorbable fibers; or

an asymmetric composite of different biodegradable and/or bioabsorbable fibers.

Preferably, the adhesion-reducing barrier contains the above described membranes.

In yet another aspect, the invention is directed to a method for reducing surgical adhesions which involves positioning an adhesion-reducing barrier between the site of surgical activity and neighboring tissues. The barrier contains a biodegradable and/or bioabsorbable membrane, in which the membrane contains:

a composite (or an asymmetric composite) of different biodegradable and/or bioabsorbable fibers;

a plurality of layers, with at least two layers having different biodegradable and/or bioabsorbable fibers from each other; or

sub-micron diameter biodegradable and/or bioabsorbable fibers, having at least one medicinal agent contained within the fibers.

Preferably, the method involves use of the above described barriers.

In yet another aspect, the invention is directed to a system for controlled delivery of a medicinal agent which contains the medicinal agent to be delivered and a biodegradable and/or bioabsorbable fibrous article physically associated with the medicinal agent to release the agent at a controlled rate. The article contains a composite of different biodegradable and/or bioabsorbable fibers or an asymmetric composite of different biodegradable and/or bioabsorbable fibers.

Preferably, the system will include the articles and biodegradable and/or bioabsorbable materials discussed above.

In another aspect, the invention is directed to a method for the controlled delivery of a medicinal agent which involves implanting at a target site in an animal, a system for controlled delivery of a medicinal agent. The system for controlled delivery of a medicinal agent contains the medicinal agent to be delivered and a biodegradable and/or bioabsorbable fibrous article physically associated with the medicinal agent to release the agent at a controlled rate. The article contains a composite of different biodegradable and/or bioabsorbable fibers or an asymmetric composite of different biodegradable and/or bioabsorbable fibers.

Preferably, the method involves use of the above described system.

The present invention provides biodegradable and/or bioabsorbable fibrous articles, e.g. membranes, having improved performance and handling characteristics for medical applications, including improved performance in preventing adhesions. The invention also provides fibrous articles containing fibers of controlled size and having controlled morphology and biodegredation rate with utility in a controlled delivery system.

Additional objects, advantages and novel features of the invention will be set forth in part in the description and examples which follow, and in part will become apparent to those skilled in the art upon examination of the following, or may be learned by practice of the invention. The objects and advantages of the invention may be realized and attained by means of the instrumentalities and combinations particularly pointed out in the appended claims.

BRIEF DESCRIPTION OF THE FIGURES

FIG. **1** is a schematic of an electrospinning system.

FIG. **2** is a schematic of an array of spinnerets for an electrospinning process.

FIG. **3**(*a*) is a side view schematic of a multiple spinneret system for producing membranes in accordance with the invention.

FIG. **3**(*b*) is a cross-sectional view of the spinneret system of FIG. **3**(*a*) as seen along viewing lines IV—IV thereof.

FIG. **3**(*c*) is a bottom view of the multiple spinneret system of FIG. **3**(*a*).

FIG. **4** is an SEM of a PLA-co-PGA membrane spun from a solution containing 1 wt % KH_2PO_4.

FIG. **5** is an SEM of a PLA-co-PGA membrane spun from a solution without salt added.

FIG. **6** is an SEM of a membrane described in Example 1.

FIG. **7** is an SEM of a membrane described in Example 4.

FIG. **8** is a graph of the results of the drug release test described in Example **4**.

FIG. **9** is an SEM of a PLA membrane described in Example 5.

FIG. **10** is a graph of the results of the biodegradation tests described in Example 6.

FIG. **11** is an SEM of the PLA membrane described in Example 7.

FIG. **12** is an SEM of the PLA membrane described in Example 7 after 1 week of degradation.

FIG. **13** is a graph of the results of the adhesion experiment described in Example 8.

FIG. **14** is a graph showing the tensiometer readings from the experiment described in Example 8.

FIG. **15** is a graph of the results of the antibacterial test described in Example 9.

FIG. **16** is an SEM of the as spun membrane described in Example 10.

FIG. **17** is an SEM of the partially biodegraded membrane described in Example 10.

DETAILED DESCRIPTION OF THE INVENTION

The present invention is directed to biodegradable and/or bioabsorbable fibrous articles and methods for using the articles for medical applications including reducing the formation of post-surgical adhesions between a healing trauma site and the adjacent tissue and controlled delivery systems.

In one aspect, the invention relates to a biodegradable and bioabsorbable fibrous article formed by electrospinning fibers of biodegradable and/or bioabsorbable fiberizable material in which the article contains a composite of different biodegradable and/or bioabsorbable fibers.

In another aspect, the article can contain an asymmetric composite of different biodegradable and/or bioabsorbable fibers.

In yet another aspect, the article can also include fibers of at least one non-biodegradable/non-bioabsorbable material.

By the term biodegradable is intended a material which is broken down (usually gradually) by the body of an animal, e.g. a mammal, after implantation.

By the term bioabsorbable is intended a material which is absorbed or resorbed by the body of an animal, e.g. a mammal, after implantation, such that the material eventually becomes essentially non-detectable at the site of implantation.

By the terminology "biodegradable and/or bioabsorbable fiberizable material" is intended any material which is biocompatible, as well as biodegradable and/or bioabsorbable, and capable of being formed into fibers, as described more fully below. The material is also capable of being formed into a fibrous article which is suitable for implantation into an animal and capable of being biodegraded and/or bioabsorbed by the animal.

The biodegradable and/or bioabsorbable fiberizable material is preferably a biodegradable and bioabsorbable polymer. Examples of suitable polymers can be found in Bezwada, Rao S. et al. (1997) *Poly(p-Dioxanone) and its copolymers, in Handbook of Biodegradable Polymers,* A. J. Domb, J. Kost and D. M. Wiseman, editors, Hardwood Academic Publishers, The Netherlands, pp. 29–61, the disclosure of which is incorporated herein by reference in its entirety.

In a preferred embodiment the biodegradable and/or bioabsorbable polymer contains a monomer selected from the group consisting of a glycolide, lactide, dioxanone, caprolactone, trimethylene carbonate, ethylene glycol and lysine. By the terminology "contains a monomer" is intended a polymer which is produced from the specified monomer(s) or contains the specified monomeric unit(s). The polymer can be a homopolymer, random or block co-polymer or hetero-polymer containing any combination of these monomers. The material can be a random copolymer, block copolymer or blend of homopolymers, copolymers, and/or heteropolymers that contains these monomers.

In one embodiment, the biodegradable and/or bioabsorbable polymer contains bioabsorbable and biodegradable linear aliphatic polyesters such as polyglycolide (PGA) and its random copolymer poly(glycolide-co-lactide) (PGA-co-PLA). The FDA has approved these polymers for use in surgical applications, including medical sutures. An advantage of these synthetic absorbable materials is their degradability by simple hydrolysis of the ester backbone in aqueous environments, such as body fluids. The degradation products are ultimately metabolized to carbon dioxide and water or can be excreted via the kidney. These polymers are very different from cellulose based materials, which cannot be absorbed by the body.

These materials are also effective drug carriers for pharmaceutical products, as they meet several drug release criteria including a biocompatible and biodegradable polymer matrix that provides efficient drug loading. The degradation rate of these materials, as well as the release rate of entrapped drugs, can only be roughly controlled by varying the molecular structure and the molecular weight as there is no linear relationship between the physical properties of the constituent homopolymers or their copolymers. However, by controlling the filament diameter (to nanometer sizes) and the assembly morphology as described more fully below, the degradation rate and the drug release rate can be finely tuned. For example, Dunne et al. examined the influence of processing conditions, particle characteristics and media temperature on the degradation of PGA-co-PLA spherical particles. They found that a linear relationship between the degradation rate and particle size existed, with the larger particles degrading fastest.

Other examples of suitable biocompatible polymers are polyhydroxyalkyl methacrylates including ethylmethacrylate, and hydrogels such as polyvinylpyrrolidone, polyacrylamides, etc. Other suitable bioabsorbable materials are biopolymers which include collagen, gelatin, alginic acid, chitin, chitosan, fibrin, hyaluronic acid, dextran, polyamino acids, polylysine and copolymers of these materials. Any combination, copolymer, polymer or blend thereof of the above examples is contemplated for use according to the present invention. Such bioabsorbable materials may be prepared by known methods.

Particularly useful biodegradable and/or bioabsorbable polymers include polyl-actides, poly-glycolides, polycarprolactone, polydioxane and their random and block copolymers. Examples of specific polymers include poly D,L-lactide, polylactide-co-glycolide (85:15) and polylactide-co-glycolide (75:25).

Preferably, the biodegradable and/or bioabsorbable polymers used in the articles of the present invention will have a molecular weight in the range of about 1,000 to about 8,000,000 g/mole, more preferably about 4,000 to about 250,000 g/mole.

By the terminology "composite of different biodegradable and/or bioabsorbable fibers" is intended any combination of the different fibers interleaved with each other in the form of a fibrous matrix, which can be in the form of a membrane or other three dimensional form of tailored geometry, such as a tube, rod or plug.

By the terminology "asymmetric composite of different biodegradable and/or bioabsorbable fibers" is intended a composite of different biodegradable and/or bioabsorbable fibers, having at least one of non-homogeneous porosity or assembled morphology, variations in the ratio of different fibers, progressing through different regions of the composite material. For example, with reference to a membrane containing an asymmetric composite of different biodegradable and/or bioabsorbable fibers, the porosity, morphology or variations in fibers can be varied either in a direction perpendicular to or parallel with the surface of the membrane. Thus, an asymmetric composite of different biodegradable and/or bioabsorbable fibers can have 100 percent submicron diameter fibers on a first side of the membrane, zero percent submicron diameter fibers on the opposite side, and a progressively lower percentage of submicron diameter fibers in the direction from the first side across the thickness of the membrane.

By the terminology "different biodegradable and/or bioabsorbable fibers" is intended to include fibers of different diameters, fibers of different biodegradable and/or bioabsorbable materials, or fibers of both different diameters and different biodegradable and/or bioabsorbable materials.

By the terminology "fibers of different diameters" is intended that the article will include fibers having at least two different target (or intended) diameters.

By the terminology "fibers of different biodegradable and/or bioabsorbable materials" is intended to include fibers having different chemical composition, in the form of, for example, different polymeric materials, different molecular weights of the same polymeric material, or different additives (or concentration of additives), such as medicinal agents.

In one embodiment, the article will contain different fibers having diameters in the range from a few up to about 1,000

nanometers, more preferably about 10 up to about 1000 nanometers and most preferably about 20 to about 500 nanometers.

The article can contain fibers having different diameters with a controlled percentage of sub-micron diameter fibers. Preferably, the article will contain at least about 10 wt % of sub-micron diameter fibers, more preferably at least about 20 wt %, and most preferably at least about 50 wt %.

Optionally, the fibrous article can contain at least one medicinal agent. In such a case, one or more medicinal agents may be incorporated into the fibers of the article. Preferably, the medicinal agent(s) will be mixed with the bioabsorable material, e.g., polymer, prior to formation of the fibers.

In loading the medicinal agent, the medicine may need to be dissolved in a solvent that may not be compatible with the solvent used in the electrospinning process. A block copolymer, acting as a surfactant, can then be used to circumvent this difficulty. One block that forms the micellar shell is a polymer that is compatible with the fibrous material that will be used to form the nano-fibers and the other block that has a different chemical composition is more compatible with the medicinal agent. For example, a block copolymer of PLA-co-PEO could form a micelle that is compatible with the PLA solution while the inner PEO core that is more hydrophilic can be used to load more hydrophilic medicinal agents. The micellar property and uptake capacity can be determined by the chemical composition of the blocks, the molecular architecture, the block length, and the chain length ratio of the blocks. The micelles, being compatible with the fibrous material can be incorporated into the nano-fibers during processing. Furthermore, the drug release rate can also be controlled by the micellar property. For example, a glassy core can reduce the drug release rate.

By the term "medicinal agent" is intended any substance or mixture of substances which may have any clinical use in medicine. Thus medicinal agents include drugs, enzymes, proteins, peptides, glycoproteins, hormones or diagnostic agents such as releasable dyes or tracers which may have no biological activity per se, but are useful for diagnostic testing, e.g., MRI.

Examples of classes of medicinal agents that can be used in accordance with the present invention include antimicrobials, analgesics, antipyretics, anesthetics, antiepileptics, antihistamines, anti-inflammatories, cardiovascular drugs, diagnostic agents, sympathomimetic, cholinomimetic, antimuscarinics, antispasmodics, hormones, growth factors, muscle relaxants, adrenergic neuron blockers, anti-neoplastics, immunosuppressants, gastrointestinal drugs, diuretics, steroids and enzymes. It is also intended that combinations of medicinals can be used in accordance with the present invention.

Thus, in one embodiment of the present invention focal delivery and application of a medicinal agent to the wound site is achieved. Focal application can be more desirable than general systemic application in some cases, e.g., chemotherapy for localized tumors, because it produces fewer side effects in distant tissues or organs and also concentrates therapy at intended sites. Focal application of growth factors, anti-inflammatory agents, immune system suppressants and/or antimicrobials by the membranes of the present invention is an ideal drug delivery system to speed healing of a wound or incision. Focal application of anesthetics by the articles of the present invention is an ideal drug delivery system for pain management.

In one embodiment, the above described fibrous articles are in the form of a membrane. Although the discussion that follows is directed to membranes in accordance with the invention, it should be understood that the discussion is applicable to other three dimensional articles, including, but not limited to tubes, rods, plugs, blocks, etc.

In one aspect the invention is directed to biodegradable and/or bioabsorbable membranes having a controlled biodegradation rate. The chemical composition, i.e., specific polymers or blends of polymers, the fiber diameter, the membrane morphology, the molecular weight distribution and the porosity of the membrane can be used to control the degradation and/or absorption time for the membrane. As such, the membranes containing medicinal agents within the fibers themselves are well suited as a controlled drug delivery device, since the above-mentioned factors can also be used to control the rate of release of the medicinal agent.

The membrane can also contain a plurality of fibers which have different medicinal agents or different concentrations of medicinal agents. Such membranes offer unique treatment options with combinations of medicinal agents and release profiles.

In one embodiment, the membrane can contain a plurality of biodegradable and/or bioabsorable non-woven layers. The layers can have the same or different chemical composition, fiber diameters, membrane morphology and porosity as discussed more fully above. Multiple layered membranes can offer yet another way to precisely control degradation and drug release rate.

In such an embodiment, it is also contemplated that medicinal agents can be incorporated between the layers of the multi-layered membrane, instead of or in addition to, incorporating the agents into the fiber structure itself.

In one embodiment, the membrane can be attached to a non-absorbable reinforcement layer, such as a Marlox mesh.

In another aspect, the invention relates to a fibrous article formed by elecrospinning different fibers of different materials, in which the article contains a composite of different fibers containing fibers of at least one biodegradable material and fibers of at least one non-biodegradable material.

In addition to drug delivery devices, the membranes of the present invention are particularly well suited for use as an adhesion-reducing barrier.

The membranes of the present invention may be employed as barriers between tissues or barriers between tissue and bone to prevent binding of tissue to tissue or of tissue to bone. Examples of uses of the devices of the present invention include, but are not limited to, barriers between the internal female reproductive organs (e.g., uterus, fallopian tubes, ovaries); barriers between the internal female reproductive organs and the peritoneum; barriers for use during laparoscopy; barriers between periodontal tissue; barriers between cartilage or between cartilage and bone; barriers between digestive organs; spinal barriers; barriers between digestive organs and peritoneum; barriers between the epicardium and surrounding structures such as the pericardium, mediastinal fat, pleura, and sternum; barriers between tendons and tendon sheaths, such as those in the wrist and ankle; bone fracture wraps; barriers between muscle tissue and bone; barriers between the esophagus and mediasternum; barriers between the gall bladder or pancreas and the peritoneum; and barriers for scrotal surgery.

The membranes of the present invention may also be used for guided tissue regeneration. For example, the membranes may be used to cover internal perforations, such as, for example, perforations in blood vessels, internal organs, the nasal septum, and the eardrum membrane, and may be used to reconstruct the abdominal wall, or to reinforce areas prone to or showing scar formation, such as, for example, inguinal

hernias. The membrane therefore acts as a patch for covering the perforation until complete healing, followed by copolymer absorption, is achieved. It is also contemplated that the membranes may be employed as a cover for burns, whereby the device acts as a patch until the burn is healed.

The membranes of the present invention may be employed as a scaffolding to treat ulcers. A porous membrane can be designed to stimulate the proliferation of fibrous tissue, as a consequence of which, for example, in the case of ulcers, the wound bed becomes more optimal for the regeneration of skin.

The membranes of the present invention may also be employed in redirect healing, whereby the devices are employed to protect nerves and organ coverings, and mucosa during the healing process, whereby the formation of fibrous tissue over such nerves, organs, and mucosa is prevented.

The membranes may also be employed to prevent the formation of internal blood clots after surgery or traumatic injury.

The membranes may also be employed in covering denuded epithelial surfaces or weakened areas such as damaged middle ear mucosa or other mucosal surfaces, thinned vascular walls, or surgically denuded areas, such as, for example, surgically denuded areas of the pelvis.

The membranes may also be employed as anti-fibroblastic growth barriers, or as nerve coaptation wraps for connecting or repairing severed nerve ends or for repairing inflamed nerves.

The membranes of the present invention may be formed or constructed into various shapes including, but not limited to, flat sheets, tubes, rods or other three dimensional articles, as necessary to facilitate use in a particular application.

A post surgical anti-adhesion barrier or membrane of the present invention is generally used in the form of a sheet of a desired size and shape. A surgeon may cut a custom shape from preformed sheets to suit particular applications. After the membrane is shaped for a suitable fit, the flexible nature of the membrane enables the surgeon to conform the membrane to fit around the area of injury. The membrane can be formed into a strip which wraps around the organ, e.g., an intestine, to prevent formation of adhesions. An anti-adhesion membrane according to the present invention can incorporate ties or straps which connect to the membrane and which are used to tie or otherwise secure the membrane to an area of injury. It is further contemplated that the anti-adhesion membranes of the present invention may be affixed to the wound site by surgical fasteners or sutures. The flexible nature of the present anti-adhesion membrane allows the membrane to flex and bend along with normal movements of the body without being overly restrictive.

Thus, the invention is also directed to a method for reducing post-surgical adhesions. The method involves positioning an adhesion-reducing barrier between the site of surgical activity and neighboring tissues. The adhesion-reducing barrier will contain a biodegradable and/or bioabsorbable membrane. The membrane is preferably the biodegradable and/or bioabsorbable membranes discussed above. The membrane can also be a biodegradable and/or bioabsorbable membrane which contains a plurality of layers, with at least two layers having different biodegradable and/or bioabsorbable fibers from each other or contains sub-micron diameter biodegradable and/or bioabsorbable fibers, having at least one medicinal agent contained within the fibers. Preferably, the membrane will contain an antibiotic.

All embodiments of surgical adhesion barriers or membranes as described herein are well-suited for application by techniques involving endoscopy. Endoscopic surgical procedures involve the use of cannulas or tubes which provide narrow openings into a body and allow minimally invasive access to surgical targets. In laparoscopic procedures, surgery is performed in the interior of the abdomen through small tubes inserted therein. Endoscopes are frequently used as viewing devices inserted through the cannulas which allow surgeons to see the interior of the body.

Certain endoscopic and laparoscopic procedures may require that the surgical region be insufflated. Accordingly, any instrumentation inserted into the body should be substantially sealed to ensure that gases do not enter or exit the body through the incision. Moreover, endoscopic and laparoscopic procedures often require the surgeon to operate on organs, tissues and/or vessels far removed from the incisions. Thus, instruments used in such procedures are typically long and narrow while being functionally controllable from a proximal end of the instrument.

In accordance with the present invention any apparatus for deploying and positioning any of the adhesion barriers or membranes disclosed herein may be inserted through a cannula and deposited at a target site. Once the barrier is positioned as desired, it may optionally be sutured, stapled or otherwise fastened to the target site with instruments designed to be inserted through a cannula.

Thus, in another aspect, the invention is directed to a method of reducing surgical adhesions which involves positioning an adhesion-reducing barrier between the site of surgical activity and neighboring tissue. More specific applications are discussed above.

Nanofiber Fabrication Technique for Biodegradable and/or Bioabsorbable Polymers: Electrospinning Membranes with Different Biodegradable and/or Bioabsorbable Fibers

The membranes according to the present invention are preferably produced by electrospinning using a multiple jet system. Preferably, the multiple jet system includes an array of spinnerets for introducing conducting fluid containing the biodegradable and/or bioabsrobable fiberizable material. The use of a multiple jet system to produce membranes in accordance with the invention is possible by having independent control over different jets. Thus, different jets can produce different fibers as discussed more fully above.

Moreover, sub-micron diameter fibers can be produced in accordance with the invention at a relatively high yield. For example, a 40% polymer solution being spun from a single spinneret with a diameter of 700 microns, which results in a final filament having a diameter of 250 nm, will have a draw ratio of 7.84×10^6. If the extrudate (conducting fluid) from each spinneret has a rate of about 10 μl/min, the final filament speed will be about 136 m/s for each spinneret, which is a relatively high spinning rate. Thus, a commercially viable process for making membranes according to the invention is achievable with a sufficient number of spinnerets operating at such speeds.

The conducting fluid will preferably include a solution of the polymer materials described more fully above. The polymer material used to form the membrane is first dissolved in a solvent. The solvent can be any solvent which is capable of dissolving the polymer and providing a conducting fluid capable of being electrospun. The solvent is preferably selected from N,N-Dimethyl formamide (DMF), tetrahydrofuran (THF), N-N-dimethyl acetamide (DMAc), methylene chloride, dioxane, ethanol, chloroform or mixtures of these solvents.

The conducting fluid can optionally contain a salt which creates an excess charge effect to facilitate the electrospinning process. Examples of suitable salts include NaCl, KH_2PO_4, K_2HPO_4,KIO_3, KCl, $MgSO_4$, $MgCl_2$, $NaHCO_3$, $CaCl_2$, or mixtures of these salts.

The polymer solution forming the conducting fluid will preferably have a polymer concentration in the range of about 1 to about 80 wt %, more preferably about 10 to about 60 wt %. The conducting fluid will preferably have a viscosity in the range of about 50 to about 2000 mPa·s, more preferably about 200 to about 700 mPa·s.

The electric field created in the electrospinning process will preferably be in the range of about 5 to about 100 kilovolts (kV), more preferably about 10 to about 50 kV. The feed rate of the conducting fluid to each spinneret (or electrode) will preferably be in the range of about 0.1 to about 1000 microliters/min, more preferably about 1 to about 250 microliters/min.

A particular apparatus for producing membranes according to the present invention, which uses a multiple jet electrospinning system, is shown schematically in FIG. **1**. Equipment not essential to the understanding of the invention such as heat exchangers, pumps and compressors and the like are not shown.

Referring now to FIG. **1**, the conducting fluid, which contains the biodegradable polymer, is supplied by a micro-flow pump system **1**. The conducting fluid preferably contains a biodegradable polymer, a solvent and a salt, e.g., 25 wt % PLA-DMF solution with 1 wt % KH_2PO_4. Optionally, one or more medicinal agents can be incorporated into the conducting fluid. The pump system **1** is linked to a computer **2** which controls the flow rate of the conducting fluid to selected spinnerets by controlling pressure or flow rate. The flow rate can be changed depending upon the speed of the support membrane **3** and the desired physical characteristics of the membrane, i.e., membrane thickness, fiber diameter, pore size, membrane density, etc.

The pump system **1** feeds the conducting fluid to a multiple jet system **4** that contains manifolds **5** having a bank of spinnerets **6**. A charge in the range of about 20 to about 50 kV is typically applied to the spinnerets by a high voltage power supply **7**. A hood **8** is positioned over the multiple jet system **4** to remove the solvent at a controlled evaporation rate.

A ground plate **9** is positioned below the multiple jet system **4** such that an electric field is created between the charged spinnerets **6** and the ground plate **9**. The electric field causes tiny jets of the conducting fluid to be ejected from the spinnerets and spray towards the ground plate **9**, forming small, e.g., sub-micron, diameter filaments or fibers.

A moving support **3** is positioned between the charged spinnerets **6** and the ground plate **9** to collect the fibers which are formed from the spinnerets and to from an interconnected web of the fibers. The support **3** moves in the direction from the unwind roll **10** to the rewind roll **11**.

The micro-flow control/pumping system is electrically isolated from the ground and is powered by an isolation transformer **12**.

The post-spinning processors **13** have the functions of drying, annealing, membrane transfer (for example, from a stainless steel mesh substrate to another substrate, e.g., a Malox mesh) and post conditioning.

Multiple jets with designed array patterns can be used to ensure the fabrication of uniform thickness of the membrane. Hood, heating and sample treatment chambers can also be included to control the solvent evaporation rate and to enhance the mechanical properties. The recovered thickness can be precisely controlled from tens of microns to hundreds of microns. While additional embodiments or modifications to the electrospinning process and apparatus are described below, a more detailed description of an apparatus and method for electrospinning polymeric fibers is set forth in co-pending, commonly owned patent application, Ser. No. 09/859,004, entitled "Apparatus and Methods for Electrospinning Polymeric Fibers and Membranes," filed 05/16/2001, now U.S. No. 6,703,011.

Variation of Electric/Mechanical Properties of Conducting Fluid

The properties of the resulting membrane produced by electrospinning will be affected by the electric and mechanical properties of the conducting fluid. The conductivity of the macromolecular solution can be drastically changed by adding ionic inorganic/organic compounds. The magneto-hydrodynamic properties of the fluid depend on a combination of physical and mechanical properties, (e.g., surface tension, viscosity and viscoelastic behavior of the fluid) and electrical properties (e.g., charge density and polarizability of the fluid). For example, by adding a surfactant to the polymer solution, the fluid surface tension can be reduced, so that the electrostatic fields can influence the jet shape and the jet flow over a wider range of conditions. By coupling a pump system that can control the flow rate either at constant pressure or at constant flow rate, the effect of viscosity of the conducting fluid can be controlled.

Electrode Design

In another method for producing membranes according to the present invention, the jet formation process during electrospinning is further refined to provide better control over fiber size. Instead of merely providing a charged spinneret and a ground plate, a positively charged spinneret is still responsible for the formation of the polymer solution droplet and a plate electrode with a small exit hole in the center is responsible for the formation of the jet stream. This exit hole will provide the means to let the jet stream pass through the plate electrode. Thus, if the polymer droplet on the positively charged spinneret has a typical dimension of 2–3 mm and the plate electrode is placed at a distance of about 10 mm from the spinneret, a reasonable electrostatic potential can be developed. The short distance between the two electrodes implies that the electrostatic potential could be fairly low. However, the resultant electric field strength could be sufficiently strong for the electrospinning process. By varying the electric potential of individual spinnerets, the jet formation can be controlled and adjusted for individual spinnerets. Such an electrode configuration should greatly reduce the required applied potential on the spinnerets from typically about 15 kilovolts (kV) down to typically about 1.5 to 2 kV (relative to the ground plate potential). The exact spinneret potential required for stable jet formation will depend on the electric/mechanical properties of the specific conducting fluid.

Control of Jet Acceleration and Transportation

In another method for producing membranes according to the present invention, the jet stream flight of individual spinnerets is also precisely controlled. The jet stream passing through the plate electrode exit hole is positively charged. Although this stream has a tendency to straightening itself during flight, without external electric field confinement the jet will soon become unstable in its trajectory. In other words, the charged stream becomes defocused, resulting in loss of control over the microscopic and macroscopic properties of the fluid. This instability can be

removed by using a carefully designed probe electrode immediately after the plate electrode and a series of (equally) spaced plate electrodes. The electrode assembly (i.e., the probe electrode and the plate electrodes) can create a uniform distribution of electrostatic potential along the (straight) flight path. The acceleration potential is formed by placing the base potential of the spinneret at about +20 to +30 kV above the target (at ground potential) while the electrostatic potential of the probe electrode can be adjusted to slightly below the plate electrode base potential. The composite electrodes are capable of delivering the jet stream to a desired target area.

Jet Manipulation

In yet another method for producing membranes according to the present invention, individual jet streams can be focused by using an "Alternating Gradient" (AG) technique. The basic idea is to use two pairs of electrostatic quadrupole lenses. The second lens has the same geometric arrangement as the first lens with a reversed (alternate) electric gradient. The positively charged jet stream will be focused, for example, in the xz plane after the first lens and then be refocused in the xz plane after the second lens. It is noted that the z-direction represents the direction of the initial flight path. By applying an additional triangle-shaped waveform to the potential on one of the pairs of the quadrupole, the jet can be swept across the target area, allowing the control of the direction of the jet stream. Furthermore, with varying waveform of the 'sweep' potential, a desired pattern on the target can be formed.

Pattern Design by Electrospinning

In yet another method for producing membranes according to the present invention, reference will be made to FIG. **2**. In this method, the conducting fluid is introduced into the electrospinning process through an array of electrospinning spinnerets **20**. The array of electrospinning spinnerets are assembled in a matrix **21** that provides electrical isolation for the spinnerets, with each spinneret having two pairs (X and Y direction) of miniature scanning electrodes **22**. The spinneret **20** and the scanning electrodes **22** are electrically wired such that each individual polymer solution jet can be turned on and off and be steered to a finite size target area. As each spinneret **20** can be turned on/off independently by electricity, the response time will be relatively fast. Also, each spinneret **20** can deliver a different solution, e.g., each containing a different polymer or different drug or concentration of drug. A designed pattern can be obtained in the resultant membrane. This pattern can be precisely controlled by a computer and can be tailored for specific medical applications.

Multiple Jet Slit-Die Geometry

In another apparatus for producing membranes in accordance with the present invention, reference is made to FIGS. **3**(*a*)–**3**(*c*). In this apparatus, a multiple jet system **30** comprises an array of electrospinning spinnerets **31**, each spinneret **31** being defined by a slit **32** formed in a slit-die **33** that is coupled to high voltage to serve as an electrode disposed above the ground plate **34**. As shown in detail in FIG. **3**(*c*), the spinnerets **31** are each interconnected by selectively narrow slits **35**, such that each spinneret **31** is interconnected to a neighboring spinneret **31** by a slit **35**. The conducting fluid will not flow through the slits **35**, but will flow through each of the spinnerets **31** in a more robust manner.

The slit-die approach permits three distinct advantages that are not available by using individual spinnerets. (1) The slit-die is made up of two separate components with controlled dimensions of the effective openings for the spinnerets. In other words, by changing the distance between the two components, the effective openings of the spinnerets become available. (2) The presence of slits between the larger openings permits fluid flow and thereby equalizes the pressure difference between the spinnerets. (3) The presence of slits can also reduce potential blockage of the fluid.

The membranes produced by the slit-die approach can achieve a larger degree of flexibility in the structures. For example, different size nanofibers can be produced from the same slit-die setup.

Control of Degradation Rate Through Processing Parameters

As discussed above, very different fiber diameter and morphology in the membrane can be obtained by changing the parameters in the electrospinning process. As the degradation rate is inversely proportional to the fiber diameter, the manipulation capability through processing parameters provides not only the means to control the degradation rate of the membrane but also the ways to control drug loading efficiency and the drug release rate.

For example, it is believed that a change in charge density (through the addition of salts) can significantly affect the fiber diameter. When 1 wt % potassium phosphate (KH_2PO_4) was added to a PLA-co-PGA solution, the fiber diameter became much thinner (see SEM picture in FIG. **4**) than the one with no salt added (FIG. **5**). Thus, it is believed that higher excess charge density generally favors the production of thinner fibers and lower excess charge density favors the production of thicker fibers. Several other kinds of salts (e.g. NaCl, KH_2PO_4, KIO and K_3PO_4), which are all biologically compatible to the body, are also contemplated.

Control of Drug Release Rate and Test of Antibacterial Effect

It is also believed that when a drug is incorporated into the fibers of the membrane, the drug release rate is a function of fiber diameter. As such, the release rate of a drug trapped in the membrane can be precisely controlled. Many surgical procedures often lead to adhesion formation involving the colon and rectum. This additionally increases the risk of post-operative infection. The addition of antibiotics to the membrane with scheduled release may be used to reduce the risk of abscess and infection.

EXAMPLES

The following non-limiting examples have been carried out to illustrate preferred embodiments of the invention. These examples include the preparation of membranes according to the invention, analysis of the membranes and testing of the membranes.

Example 1

A membrane was prepared as follows: a 30 wt % PLG copolymer/DMF solution was prepared by slowly dissolving PLG copolymer pellets (inherent viscosity of 0.55–0.75. Birmingham Polymers Inc., AL) into an N,N-dimethyl formamide (DMF) solvent at room temperature. The solution was then loaded into the 5 ml syringe fitted with a gauge 20 needle, and delivered through a Teflon tube (0.03" ID) to the exit hole of an electrode having a diameter of 0.025". The solution was pumped and controlled by a syringe pump (Harvard Apparatus "44" series, MA) at a flow rate of 20 microliters/min. A 25 kV positive high voltage (by Glassman High Voltage Inc.) was applied on the electrode. The dis-

tance from the tip of the electrode to the grounded collecting plate was 15 cm. A tiny electrospinning jet was formed and stabilized in 30 seconds under these conditions. The collecting plate was movable and controlled by a stepper motor. The collecting plate was continually moved at a rate of 1 mm/sec until a membrane having a relatively uniform thickness of about 100 microns was obtained. An SEM (Scanning Electron Microscopy) image of the membrane is shown in FIG. **6**.

Example 2

A biodegradable and bioabsorbable membrane according to the present invention, fabricated by a multi-jet electrospinning process, was prepared as follows: an 8 wt % polyacrylonitrile (Aldrich Chemical Company, Inc.)/DMF solution was prepared by slowly adding and dissolving the polymer powders into an organic solvent, which was DMF (N,N-dimethyl formamide), at room temperature. After the solution was completely mixed, it was then loaded into 6 individual syringes, each with a volume of 5 mL. The syringes were fitted with gauge 20 needles and the solution was delivered through Teflon tubes (0.03" ID) to 6 electrodes, each having a tiny hole with a diameter of 0.025". The polymer solution was finally pumped and controlled by a syringe pump (Harvard Apparatus "44" series, MA) at a flow rate of 25 microliters/min. In addition, a 26 kV positive high voltage (by Glassman High Voltage Inc.) was applied on the electrodes in order to obtain the existence of six well-stabilized electrospinning jets. The distance from the tip of the electrodes to the grounded collecting plate was 15 cm and the tips of the electrodes were spaced about 2 cm apart from each other. Closer spacing between electrodes (spinnerets) could have been achieved by changing appropriate parameters, e.g., by increasing the applied electric potential. The collecting plate was movable and controlled by a step motor. The collecting plate was continually moved at a rate of 1 mm/sec until a bioabsorable and biodegradable membrane having a relatively uniform thickness of about 100 microns was obtained.

Example 3

A polymer solution suitable for electrospinning, which contained a drug, was prepared as follows: A sample of Poly(DL-lactide) ("PLA") purchased from Birmingham Polymers, Inc., Birmingham, Ala. (Product No. D98120) having a weight average molecular weight of 1.09×10^5 g/mole and a polydispersity of 1.42 was stored in a vacuum oven at room temperature. The pellets were dissolved in DMF purchased from Fisher Scientific, Fair lawn, N.J. to form a 25 wt % solution. The antibiotic drug used was Mefoxin™ from Merck & Co., Inc., West Point, Pa. The antibiotic was dissolved in distilled water and then mixed with PLA/DMF solution in appropriate amounts to form the solution with a PLA/drug ratio of 9:1. A stable jet was formed using this solution in the electrospinning process described in Example 1.

Example 4

A second membrane was prepared in a similar manner to Example 1, except that a drug solution was added to the polymer solution prior to electrospinning and the voltage applied to the electrode was adjusted. The drug solution was prepared by dissolving 0.6 grams of Mefoxin (Merck & Co Inc.) into 0.4 grams of water. The drug solution was then very slowly (dropwise) added to the polymer solution with gentle stirring until it reached a final PLG/drug ratio of 19:1. A 20 kV positive high voltage (by Glassman High Voltage Inc.) was applied on the electrode. All other parameters were the same as Example 1. An SEM (Scanning Electron Microscopy) image of the membrane containing the drug is shown in FIG. **7**.

The drug release rate was determined by placing the membrane in a phosphate buffer solution (PBS) and then by monitoring the drug concentration in the buffer solution vs. time using an ultra violet (UV) light (234 nm) absorption measurement. The drug release (in PBS buffer) profile is shown in FIG. **8**.

Example 5

A membrane was fabricated as follows: A 35 wt % PLA polymer/DMF solution was prepared by slowly dissolving the PLA pellets. The solution was fed through the syringe pump system to the electrodes at a flow rate of 20 microliters/min per jet. A 25 kV positive high voltage was applied to the electrode. FIG. **9** shows a typical scanning electron microscopy (SEM) image of an electrospun PLA membrane made by the procedures described above. It has an average fiber diameter of 200 nm. The typical membrane density is about 0.25 g/cm^3, as compared to the neat resin (PLA) density of 1.3 g/cm^3.

Example 6

An in-vitro biodegradation test was conducted to evaluate the performance of electrospun membranes. The biodegradation test was conducted using the following method, which is routinely used in the suture industry: a PGA membrane was submerged in a buffer solution containing sodium phosphate, potassium phosphate, and distilled water (pH 7.3), and maintained at 37° C. The weight loss was measured as a function of time. The test was repeated for a PLA membrane. The results for both membranes are plotted in FIG. **10**. A review of FIG. **10** reveals that the major weight loss (50%) varies from 2 weeks (PGA) to about 6 months (PLA).

Example 7

A membrane containing dual thickness fibers was prepared as follows: a 25 wt % PLA-DMF solution was prepared by slowly dissolving PLA polymer pellets having the same molecular weight and poly dispersity as in Example 3 into a DMF solvent. A drug solution was prepared by dissolving 0.6 grams of Mefoxin (Merck & Co Inc.) into 0.4 grams of water. The drug solution was then very slowly (dropwise) added to the polymer solution with gentle stirring until it reached a final PLA/drug ratio of 19:1. A 20 kV positive high voltage (by Glassman High Voltage Inc.) was applied on the electrode. All other parameters were the same as Example 1. A membrane having a network structure consisting of large size filaments (2 micron diameter), very fine fibrils (50 nanometer diameter) and small blobs was obtained by varying the solution feed rate over a range from 20 μl/min to 70 μl/min. An SEM of the resulting membrane is shown in FIG. **11**.

The membrane was then placed in the buffer solution described in Example 6. After one week of degradation in the control buffer, the fine fibers completely disappeared (FIG. **12**). A comparison of FIGS. **11** and **12** reveals that this morphology results in a rapid weight loss in the first week.

Thus, if more rapid weight loss is desired, a membrane having a higher concentration of thin fibrils can be produced.

Example 8

An experiment was conducted to evaluate the barrier properties of different membranes for preventing post-operative induced adhesions. The experiment used an objective rat model (ORM) to evaluate the performance of electrospun PLA-co-PGA membranes, with and without an antibiotic drug (Mefoxin) contained in the membrane structure, which were prepared in the same manner as in Examples 1 (without the drug) and 4 (with the drug). A control group was also used for comparison.

The test procedures used were as follows: the membrane being tested was first sterilized using ^{60}Co radiation source. The membrane sample was sealed in a plastic bag in a container filled with dried nitrogen gas. The package then received γ-radiation doses from 5.15~25 kGy, depending on the mass. This procedure has been well documented in the literature.

300–450 gram male Sprague-Dawley rats were used in the experiments. They were individually housed and given food and water ad libitum both pre- and postoperatively. Anesthesia was produced using an IM ketamine (80 mg/kg) and xylaxine (10 mg/kg) injection into the right hindleg prior to the celiotomy. Euthanasia was performed using intracardiac injection of pentobarbital (60 mg/kg).

The rats were divided into two procedure groups. The first group underwent a midline celiotomy and the cecum identified and scored using an abrasive pad until serosal bleeding was noted on the anterior surface. A1×1 cm square of abdominal wall muscle was then excised directly over the cecal wound. The first group experiment was conducted using 12 animals with the membrane and 14 animals with the membrane containing antibiotics, which were compared to 12 control animals (cecal abrasions and buttons without any membrane). The celiotomy was then closed in two layers immediately (control, n=12), after a barrier was laid in between the cecum and the abdominal wall (n=12), or after an antibiotic-impregnated barrier was placed in the aforementioned are (n=14). All rats underwent a second celiotomy after 4 weeks. The presence or absence of adhesions from the cecum to the abdominal wall was noted. The cecum was then isolated from the rest of the bowel and the breaking strength of the adhesion was measured by using a tensiometer.

In the first group of experiments, cecal adhesions were noted in 67% of the control set, 50% of the set with barriers, and 38% of the set with barriers impregnated with antibodies (see FIG. **13**). Tensiometer readings on those adhesions present were found to be 6.18, 5.76, and 4.30 respectively (see FIG. **14**). Only adhesions from the cecum to the abdominal wall were counted. Adhesional bands between the bowel and other abdominal organs were noted on occasion, but were not taken into account.

In the second group experiment, Marlex mesh, a material often used in abdominal surgery to repair the abdominal wall, was used to test the membranes. This mesh has the severe complication of causing adhesions to the intestines which not only leads to bowel obstruction, but also fistula formation. Both complications can be devastating to patients. The Marlex mesh was applied to a defect created in the abdominal wall and 10 animals had the barrier membrane interposed between the mesh and the intestines, while 10 controls had the Marlex placed with no interposing membrane. The second group of rats had Marlex mesh placed into the abdominal cavity. The abdomen was opened using a midline celiotomy and a 1×1 cm square of Marlex mesh was placed over the cecum and fixed to the abdominal wall using two silk sutures. The abdomens were then either immediately closed in two layers (control, n=10) or had a barrier placed in between the cecum and the mesh (n=10). All animals underwent a second celiotomy after 4 weeks. The presence or absence of adhesions between the cecum and mesh were noted.

In the group of rats with Marlex mesh, the first set of rats all has adhesions from the cecum to the mesh (100%). The mesh also has a multitude of other adhesions to the omentum, stomach, and liver making a measurement of adhesional strength from cecum to abdominal wall problematic. The set with barriers was found to have only one rat with adhesions from the cecum to the abdominal wall (10%).

Overall, the test results showed good barrier properties of the membranes, i.e., a low incidence of induced adhesion in the membrane embedded area, while an adhesion was induced in the control area. The membrane containing the antibiotic showed better barrier properties than the membrane without the antibiotic.

Example 9

The antibacterial effect of drug containing membranes was tested using the following procedures: 8 ml of Luria Broth (LB) and 80 microliters of *E. coli* cells were added to each of four sample test tubes. A 7.0×7.0 cm sample of a PLA electrospun membrane having a thickness of about 75 microns (with a corresponding total weight of 100 mg) was added to one of the test tubes. A second sample of a PLA membrane containing approximately 4.83 mg of Mefoxin was added to another test tube. A third sample of a PLA membrane containing approximately 8.85 mg of Mefoxin was added to a third test tube. The last test tube was used as a control.

LB was used to grow the *E. coli* bacterial cells. The sample tubes were placed in an incubator overnight. The temperature of the incubator was set at 37° C. and the shaking rate was set at 225 rpm. Shaking was necessary in order for the *E. coli* bacteria to receive enough nutrients needed to grow. Using a SmartSpec *3000 instrument, the optical density (OD) at the 600 nm wavelength for *E. coli* bacteria was recorded and the amount of cells in each test tube was calculated. The cell concentration could be related to the product of the optical density of each sample and a conversion factor. As the optical density increases (the broth becomes more turbid), the cell concentration should increase. The results are shown in FIG. **15**, with the y-axis unit being cell/ml or the bacteria concentration.

A review of FIG. **15** reveals that the growth of *E. coli* bacteria is completely prohibited by the release of the Mefoxin antibiotic drug from the membrane containing 8.85 mg of the drug. Also, it appears that the higher the loading concentration of Mefoxin, the more effective the membrane becomes.

Example 10

An in-vivo biodegradation test was conduced using a PLA electrospun membrane having an average fiber diameter in the range of about 100–150 nanometers. The membrane was fabricated as follows. A 25 wt % PLA solution in DMF was prepared. A 60 wt % Mefoxin drug in aqueous solution was then added to the polymer solution to reach a final PLA/drug ration of 9:1. A 20 kV positive voltage was applied to the

electrode. An SEM of the initial as spun membrane (FIG. **16**) shows smooth fibrous structures with an average fiber diameter between 100–150 nm. The membrane was implanted into a rat and removed after one week, following the procedures described in Example 8. An SEM of the partially biodegraded membrane is shown in FIG. **17**.

A comparison of FIGS. **16** and **17** reveals that the morphology of the membrane has been changed, resulting in a more porous structure.

Example 11

A bioabsorbable composite membrane consisting of two polymer components of different hydrophobicity according to the present invention was prepared as follows: First, a 6 wt % polyethylene oxide (PEO)/DMF solution was prepared by slowly adding the polymer powders into an organic solvent, which was DMF (N,N-dimethyl formamide). Second, a 30 wt % polylactide glycolide (PLG)/DMF solution was made by dissolving the polymers into DMF as well. After these two solutions were each completely homogenized at the room temperature, they were then loaded separately into two individual syringes, each with a volume of 5 mL. Next, the syringes were fitted with 2 gauge 20 needles and delivered through Teflon tubes to the electrodes, each having a tiny hole with a diameter of 0.025". The polymer solutions were finally pumped and controlled by a syringe pump at a flow rate of 20 microliters/min. In addition, a 25 kV positive high voltage was applied on two separate electrodes in order to obtain the existence of well-stabilized electrospinning jets. The distance from the tips of the electrodes to the ground collecting plate was 15 cm. Furthermore, a step motor was utilized in order to control the movement of the ground collector so that it was capable to move in different directions, either left or right. The collecting plate was moving at a rate of 5 steps/sec continuously until a bioabsorable membrane having a relatively uniform thickness of 100 microns was achieved.

Example 12

A bioabsorbable composite membrane consisting of two component polymer blend of different hydrophobicity according to the present invention was prepared as follows: First, a 2 wt % polyethylene oxide (PEO, Mw=100,000 g/mol)/DMF solution was prepared by slowly adding the polymer powders into an organic solvent, which was DMF (N,N-dimethyl formamide). Second, a 20 wt % polylactide glycolide (PLG)/DMF solution was made by dissolving the polymers into DMF as well. These two solutions were mixed together and were each completely homogenized at the room temperature. They were then loaded separately into two individual syringes, each with a volume of 5 mL. Next, the syringes were fitted with 2 gauge 20 needles and delivered through Teflon tubes to the electrodes, each having a tiny hole with a diameter of 0.025". The polymer solutions were finally pumped and controlled by a syringe pump at a flow rate of 20 microliters/min. In addition, a 25 Kv positive high voltage was applied on two separate electrodes in order to obtain the existence of well-stabilized electrospinning jets. The distance from the tips of the electrodes to the ground collecting plate was 15 cm. Furthermore, a step motor was utilized in order to control the movement of the ground collector so that it was capable to move in different directions, either left or right. The collecting plate was moving at a rate of 5 steps/sec continuously until a bioabsorable membrane having a relatively uniform thickness of 100 microns was achieved.

Thus, while there has been disclosed what is presently believed to be preferred embodiments of the invention, those skilled in the art will appreciate that other and further changes and modifications can be made without departing from the scope or spirit of the invention, and it is intended that all such other changes and modifications are included in and are within the scope of the invention as described in the appended claims.

We claim:

1. A biodegradable and/or bioabsorbable fibrous article formed by electrospinning fibers of biodegradable and/or bioabsorbable fiberizable material comprising a composite of different biodegradable and/or bioabsorbable fibers.

2. A fibrous article according to claim **1**, wherein said composite of different fibers is defined by fibers of different diameters.

3. A fibrous article according to claim **2**, wherein said fibers of different diameters include fibers having diameters less than 1 micron and fibers having diameters greater than 1 micron.

4. A fibrous article according to claim **3**, wherein said fibrous article comprises at least about 20 weight percent of submicron diameter fibers.

5. A fibrous article according to claim **4**, wherein said fibrous article comprises at least about 50 weight percent of submicron diameter fibers.

6. A fibrous article according to claim **1**, wherein said composite of different fibers is defined by fibers of different biodegradable and/or bioabsorbable materials.

7. A fibrous article according to claim **1**, wherein said composite of different fibers is defined by fibers of different diameters and different biodegradable and/or bioabsorbable materials.

8. A fibrous article according to claim **1**, wherein said biodegradable and/or bioabsorbable fiberizable material comprises a biodegradable and/or bioabsorbable polymer.

9. A fibrous article according to claim **8**, wherein said biodegradable and/or bioabsorbable polymer comprises a monomer selected from the group consisting of a glycolide, lactide, dioxanone, caprolactone, trimethylene carbonate, ethylene glycol and lysine.

10. A fibrous article according to claim **8**, wherein said biodegradable and/or bioabsorbable polymer comprises a biodegradable and/or bioabsorbable linear aliphatic polyester.

11. A fibrous article according to claim **10**, wherein said biodegradable and/or bloabsorbable linear aliphatic polyester is a polyglycolide or a copolymer poly(glycolide-co-lactide).

12. A fibrous article according to claim **1**, wherein said biodegradable and/or bioabsorbable fiberizable material comprises a material derived from biological tissue.

13. A fibrous article according to claim **1**, wherein said fibers have diameters in the range from about 10 up to about 1,000 nanometers.

14. A fibrous article according to claim **13**, wherein said fibers have diameters in the range from about 20 to about 500 nanometers.

15. A fibrous article according to claim **1**, further comprising small blobs of biodegradable and/or bioabsorbable material.

16. A fibrous article according to claim **1**, further comprising at least one medicinal agent.

17. A fibrous article according to claim **16**, wherein said medicinal agent is contained within said fibers.

18. A fibrous article according to claim 17, further comprising fibers with different concentrations of said medicinal agent.

19. A fibrous article according to claim 17, further comprising fibers with different medicinal agents.

20. A fibrous article according to claim 1, further comprising a plurality of layers, wherein at least one of the layers comprises a composite of different biodegradable and/or bioabsorbable fibers.

21. A fibrous article according to claim 20, further comprising at least one medicinal agent between at least two of said layers.

22. A fibrous article according to claim 1, wherein said fibrous article has a controlled degradation rate.

23. A fibrous article according to claim 1, wherein said fibrous article is a membrane.

24. A fibrous article according to claim 23, wherein said membrane has a thickness in the range of about 10 to about 5000 microns.

25. A fibrous article according to claim 24, wherein said membrane has a thickness in the range of about 20 to about 1000 microns.

26. A fibrous article according to claim 1, wherein said composite is an asymmetric composite of different biodegradable and/or bioabsorbable fibers.

27. A fibrous article according to claim 26, wherein different fibers refers to fibers of different diameters.

28. A fibrous article according to claim 27, wherein said fibers of different diameters include fibers having diameters less than 1 micron and fibers having diameters greater than 1 micron.

29. A fibrous article according to claim 28, wherein said fibrous article comprises at least about 20 weight percent of submicron diameter fibers.

30. A fibrous article according to claim 29, wherein said fibrous article comprises at least about 50 weight percent of submicron diameter fibers.

31. A fibrous article according to claim 26, wherein different fibers refers to fibers of different biodegradable and/or bioabsorbable materials.

32. A fibrous article according to claim 26, wherein different fibers refers to fibers of different diameters and different biodegradable and/or bioabsorbable materials.

33. A fibrous article according to claim 26, wherein said biodegradable and/or bioabsorbable fiberizable material comprises a biodegradable and/or bioabsorbable polymer.

34. A fibrous article according to claim 33, wherein said biodegradable and/or bioabsorbable polymer comprises a monomer selected from the group consisting of a glycolide, lactide, dioxanone, caprolactone, trimethylene carbonate, ethylene glycol and lysine.

35. A fibrous article according to claim 33, wherein said biodegradable and/or bioabsorbable polymer comprises a biodegradable and/or bioabsorbable linear aliphatic polyester.

36. A fibrous article according to claim 35, wherein said biodegradable and/or bioabsorbable linear aliphatic polyester is a polyglycolide or a copolymer poly(glycolide-co-lactide).

37. A fibrous article according to claim 26, wherein said biodegradable and/or bioabsorbable fiberizable material comprises a material derived from biological tissue.

38. A fibrous article membrane according to claim 26, wherein said fibers have diameters in the range from about 10 up to about 1,000 nanometers.

39. A fibrous article according to claim 38, wherein said fibers have diameters in the range from about 20 to about 500 nanometers.

40. A fibrous article according to claim 26, further comprising small blobs of biodegradable and/or bioabsorbable material.

41. A fibrous article according to claim 26, further comprising at least one medicinal agent.

42. A fibrous article according to claim 41, wherein said medicinal agent is contained within said fibers.

43. A fibrous article according to claim 42, further comprising fibers with different concentrations of said medicinal agent.

44. A fibrous article according to claim 42, further comprising fibers with different medicinal agents.

45. A fibrous article according to claim 26, wherein said fibrous article has a controlled degradation rate.

46. A fibrous article according to claim 26, wherein said fibrous article is a membrane.

47. A fibrous article according to claim 46, wherein said membrane has a thickness in the range of about 10 to about 5000 microns.

48. A fibrous article according to claim 47, wherein said membrane has a thickness in the range of about 20 to about 1000 microns.

49. A fibrous article formed by electrospinning different fibers of different materials, comprising a composite of different fibers which comprises fibers of at least one biodegradable material and fibers of at least one non-biodegradable material.

50. A fibrous article according to claim 49, wherein said different fibers comprise submicron diameter fibers.

51. A fibrous article according to claim 49, wherein said composite is an asymmetric composite of said different fibers.

52. A method for reducing surgical adhesions which comprises positioning an adhesion-reducing barrier between the site of surgical activity and neighboring tissue, said barrier comprising a biodegradable and/or bioabsorbable membrane, wherein said membrane comprises a composite or asymmetric composite of different biodegradable and/or bioabsorbable fibers; a plurality of layers, with at least two layers having different biodegradable and/or bioabsorbable fibers from each other; or sub-micron diameter biodegradable and/or bioabsorbable fibers, having at least one medicinal agent contained within the fibers.

53. A method according to claim 52, wherein different fibers refers to fibers of different diameters.

54. A method according to claim 52, wherein different fibers refers to fibers of different biodegradable and/or bioabsorbable materials.

55. A method according to claim 52, wherein different fibers refers to fibers of different diameters and different biodegradable and/or bioabsorbable materials.

56. A method for providing controlled tissue healing which comprises implanting at a target site in an animal, a system for controlled tissue healing, said system comprising a biodegradable and/or bioabsorbable fibrous article, wherein said fibrous article comprises a composite of different biodegradable and/or bioabsorbable fibers or an asymmetric composite of different biodegradable and/or bioabsorbable fibers.

57. A method according to claim 56, wherein said fibrous article is selected from the group consisting of a scaffold for guided tissue regeneration, a protective covering for redirecting healing, a protective covering for weakened tissue and an anti-fibroblastic growth barrier.

58. A method according to claim 56, wherein different fibers refers to fibers of different diameters.

59. A method according to claim 56, wherein different fibers refers to fibers of different biodegradable and/or bioabsorbable materials.

60. A method according to claim 56, wherein different fibers refers to fibers of different diameters and different biodegradable and/or bioabsorbable materials.

* * * * *

US006713011B2

(12) **United States Patent**
Chu et al.

(10) **Patent No.: US 6,713,011 B2**
(45) **Date of Patent: Mar. 30, 2004**

(54) **APPARATUS AND METHODS FOR ELECTROSPINNING POLYMERIC FIBERS AND MEMBRANES**

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(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) bydays.days.

(21) Appl. No.: **09/859,004**

(22) Filed: **May 16, 2001**

(65) **Prior Publication Data**

US 2002/0175449 A1 Nov. 28, 2002

(51) **Int. Cl.**[7] **D01D 5/00**; D01D 13/00; D06M 10/00

(52) **U.S. Cl.** ..... **264/465**; 264/176.1; 425/135; 425/145; 425/166; 425/174.8 E; 425/224; 425/464

(58) **Field of Search** ..... 264/176.1, 465; 425/135, 145, 166, 174.8 E, 224, 464

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Primary Examiner—Leo B. Tentoni
(74) *Attorney, Agent, or Firm*—Hoffmann & Baron, LLP

(57) **ABSTRACT**

An apparatus and method for electrospinning polymer fibers and membranes. The method includes electrospinning a polymer fiber from a conducting fluid in the presence of a first electric field established between a conducting fluid introduction device and a ground source and modifying the first electric field with a second electric field to form a jet stream of the conducting fluid. The method also includes electrically controlling the flow characteristics of the jet stream, forming a plurality of electrospinning jet streams and independently controlling the flow characteristics of at least one of the jet streams. The apparatus for electrospinning includes a conducting fluid introduction device containing a plurality of electrospinning spinnerets, a ground member positioned adjacent to the spinnerets, a support member disposed between the spinnerets and the ground member and movable to receive fibers formed from the conducting fluid, and a component for controlling the flow characteristics of conducting fluid from at least one spinneret independently from another spinneret.

50 Claims, 15 Drawing Sheets

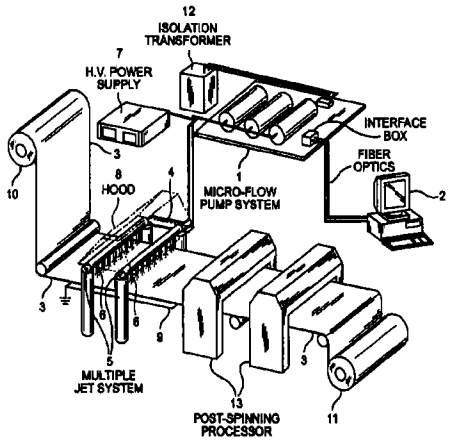


FIG. 3

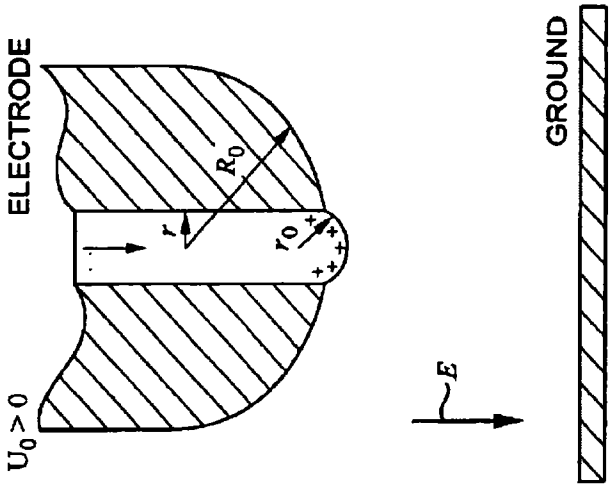


FIG. 2

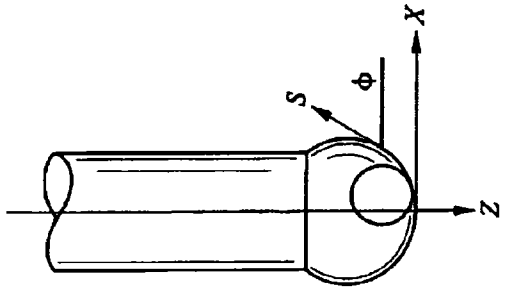
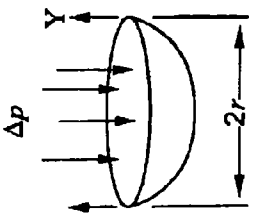


FIG. 1



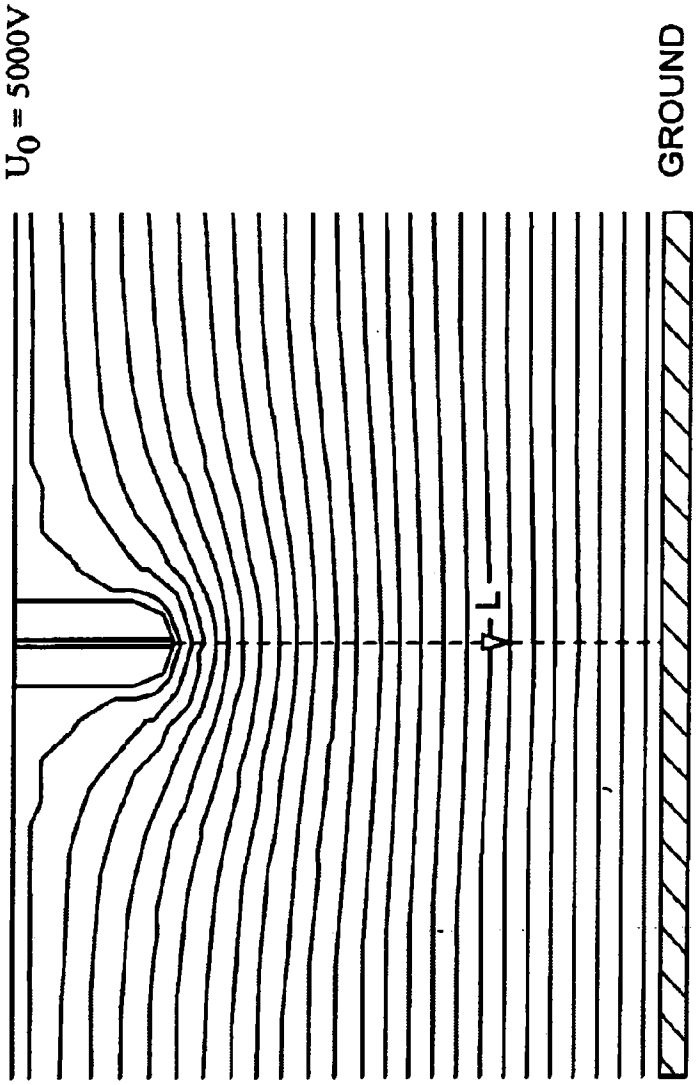


FIG. 4

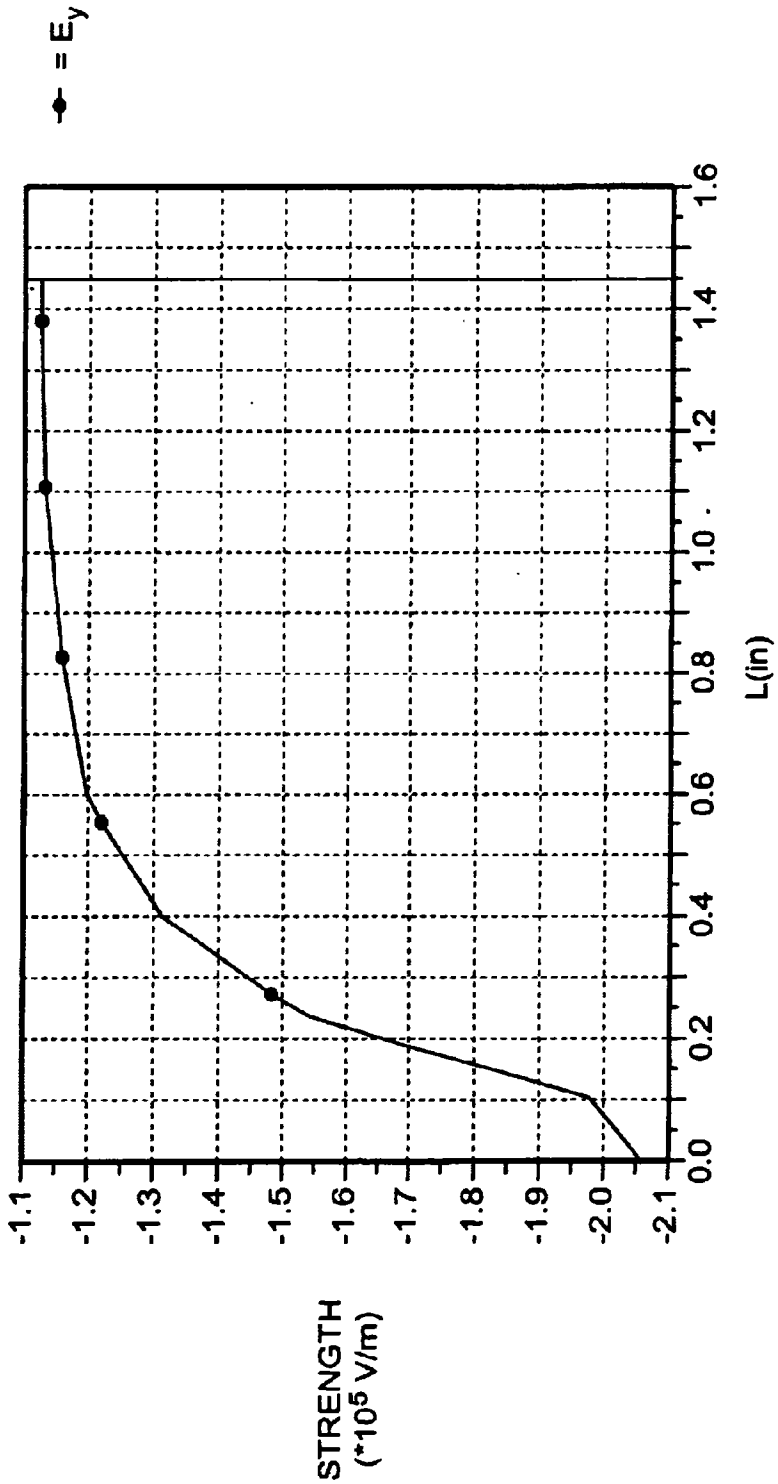

E_y
-1.1
-1.2
-1.3
-1.4
-1.5
-1.6
-1.7
-1.8
-1.9
-2.0
-2.1
STRENGTH
(*10^5 V/m)
0.0
0.2
0.4
0.6
0.8
1.0
1.2
1.4
1.6
L(in)

FIG. 5

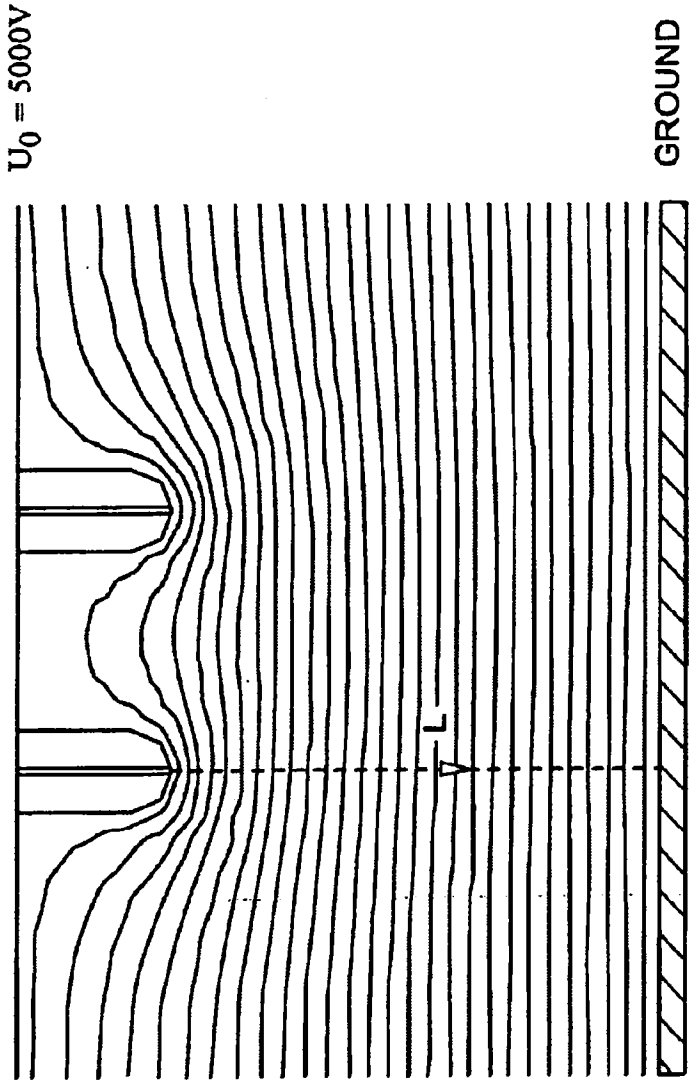
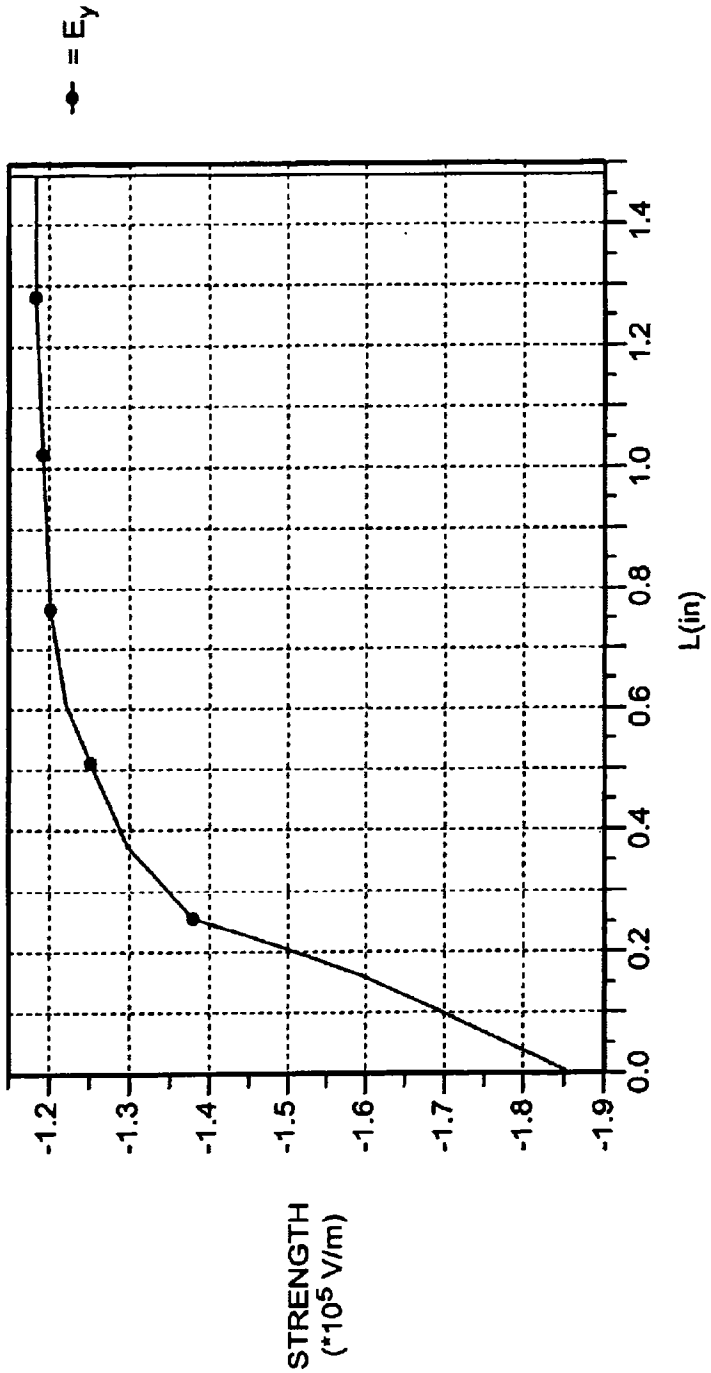


FIG. 6


= E_y
-1.2
-1.3
-1.4
-1.5
-1.6
-1.7
-1.8
-1.9
STRENGTH
(*10^5 V/m)
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0.2
0.4
0.6
0.8
1.0
1.2
1.4
L(in)

FIG. 7

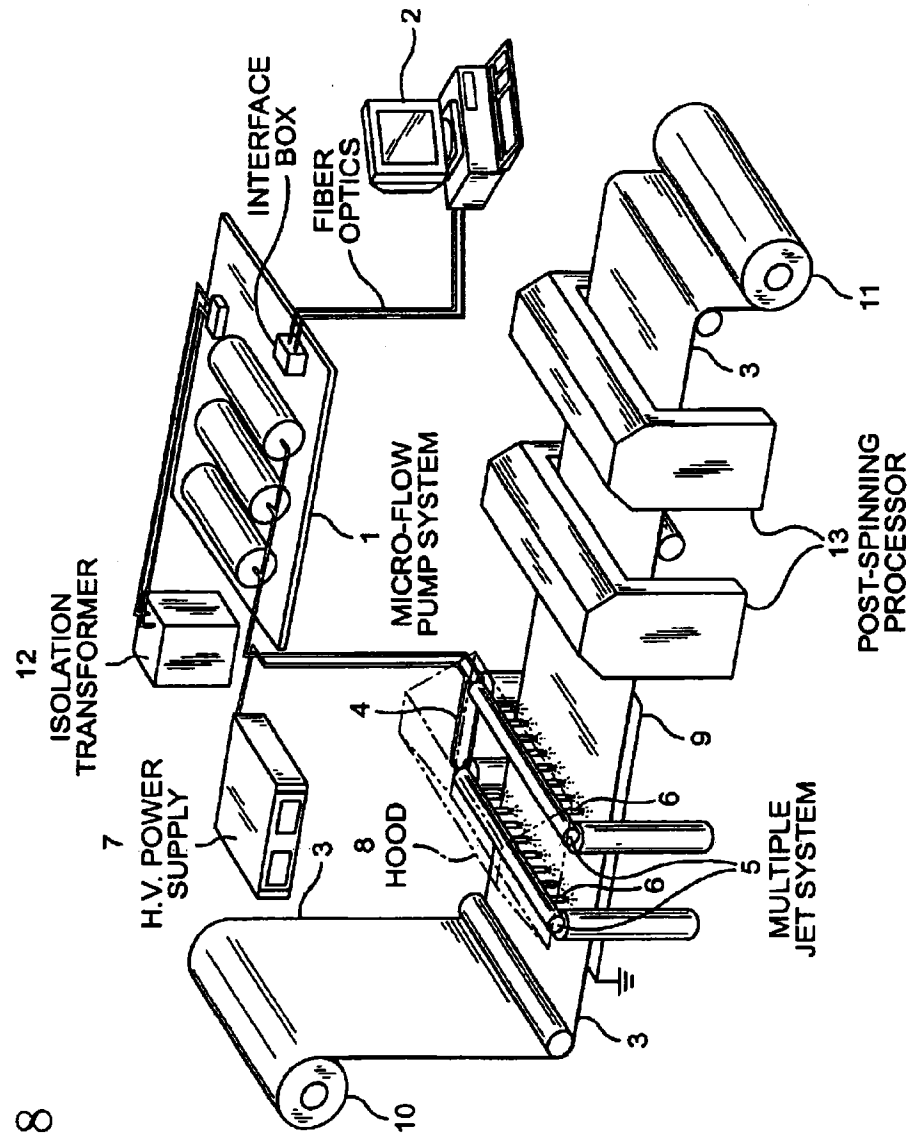
2
INTERFACE BOX
FIBER OPTICS
1
MICRO-FLOW PUMP SYSTEM
12
ISOLATION TRANSFORMER
7
H.V. POWER SUPPLY
8
HOOD
4
3
10
6
5
MULTIPLE JET SYSTEM
9
13
POST-SPINNING PROCESSOR
11

FIG. 8

FIG. 9 (a)

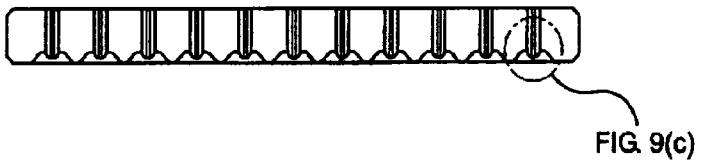

FIG. 9 (b)

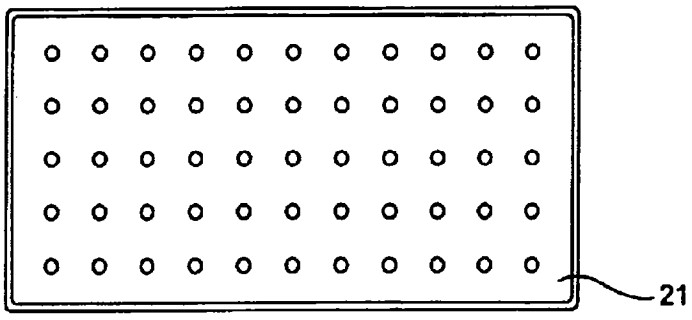

FIG. 9 (c)

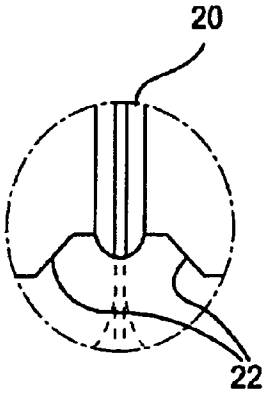

FIG. 10 (a)

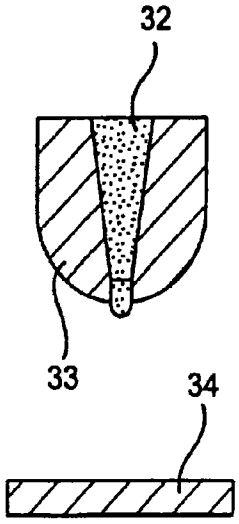

FIG. 10 (b)

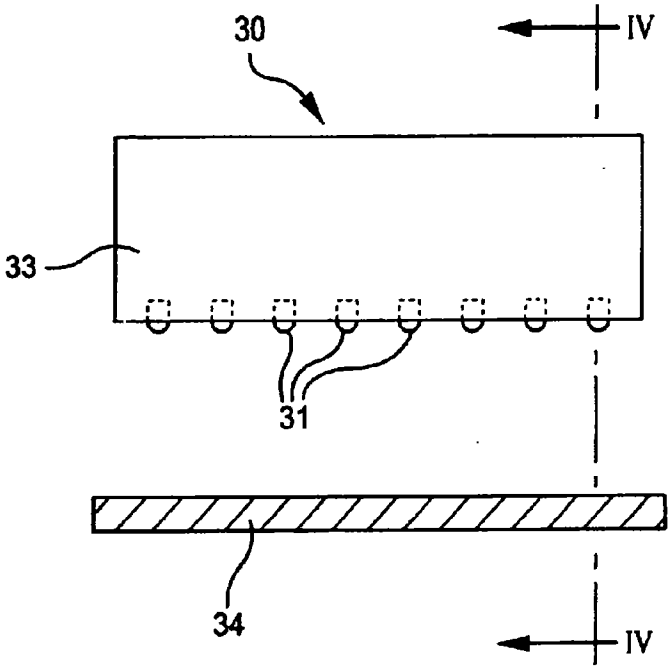

FIG. 10 (c)

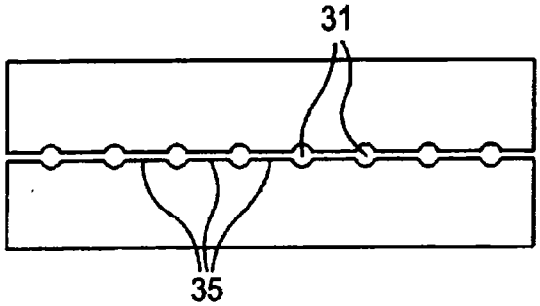

FIG. 11 SPUN MEMBRANE WITH 1 WT% KH_2PO_4

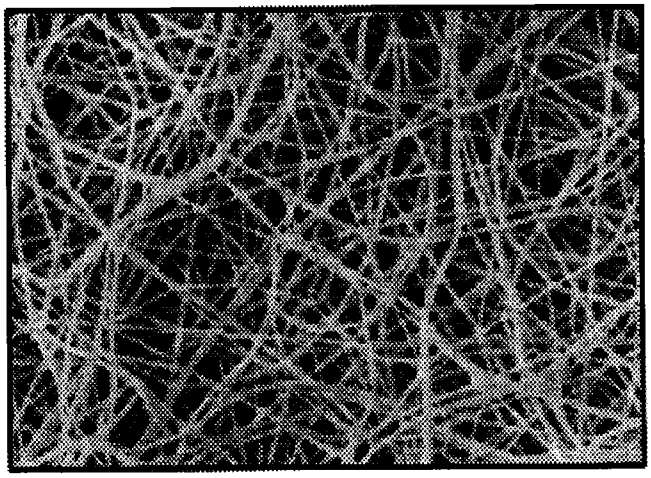

FIG. 12 SPUN MEMBRANE WITHOUT SALT

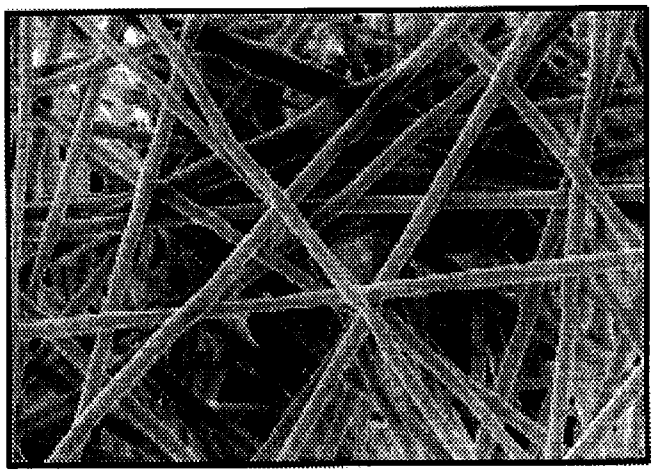

FIG. 13

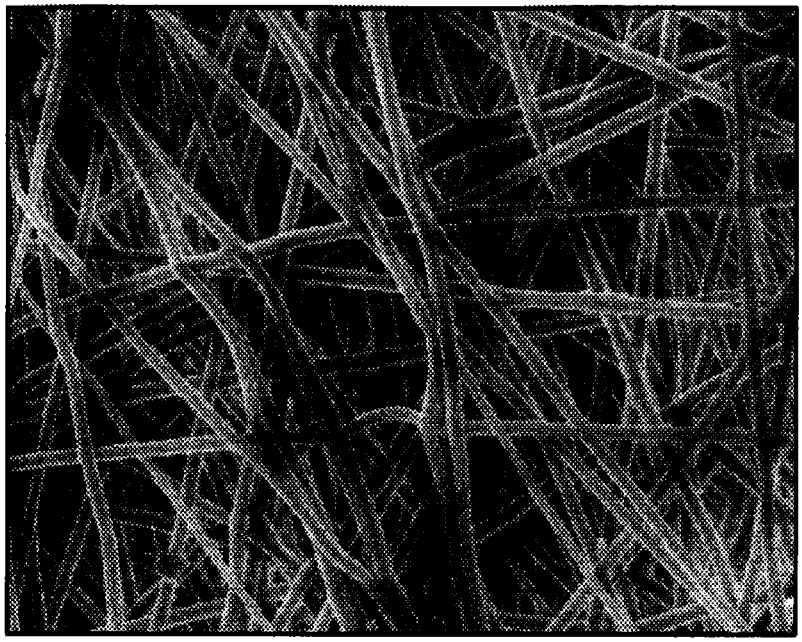

FIG. 14 SEM OF PAN MEMBRANE

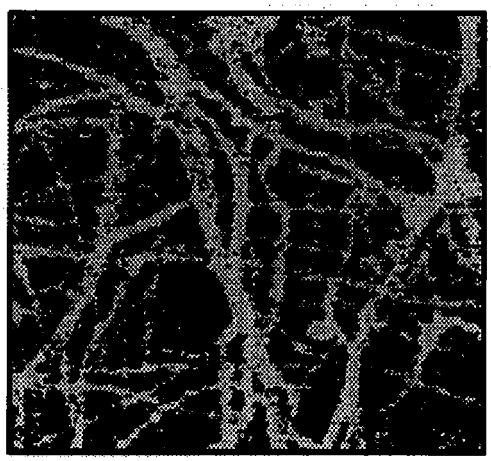

FIG. 15

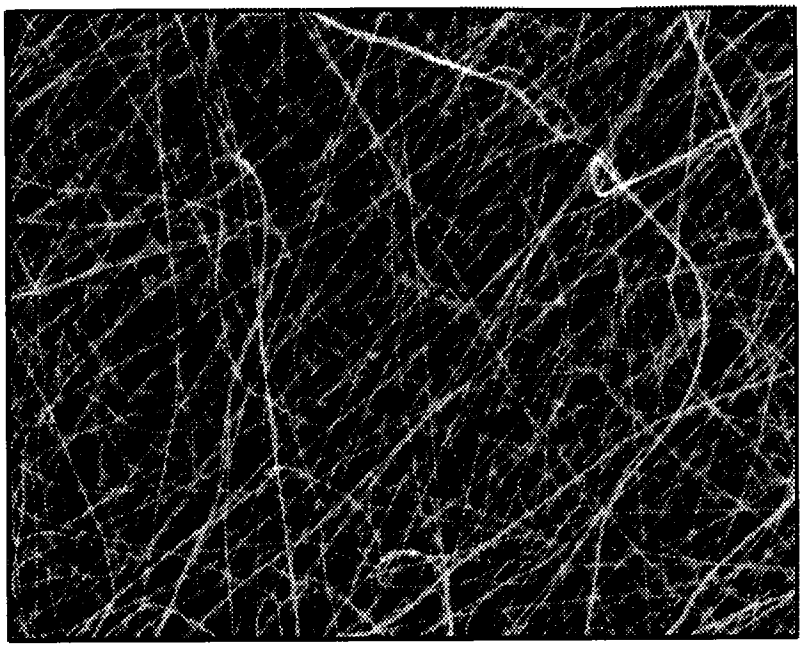

FIG. 16 SEM IMAGE OF ELECTROSPUN PLA MEMBRANE

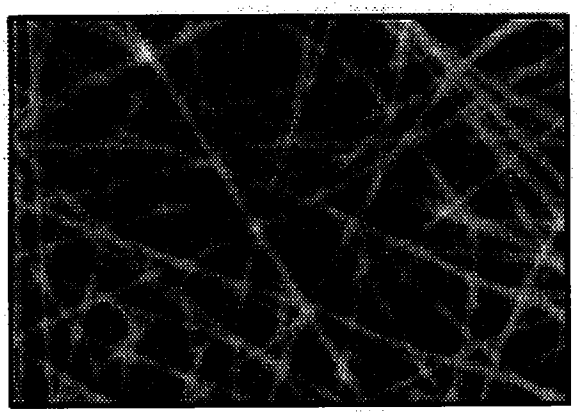

FIG. 17 DUEL THICKNESS PLA MEMBRANE

FIG. 18 SEM OF COPPER PLATED PAN MEMBRANE

APPARATUS AND METHODS FOR ELECTROSPINNING POLYMERIC FIBERS AND MEMBRANES

BACKGROUND OF INVENTION

The present invention relates to an apparatus and methods for electrospinning polymer fibers and membranes.

Electrospinning is an atomization process of a conducting fluid which exploits the interactions between an electrostatic field and the conducting fluid. When an external electrostatic field is applied to a conducting fluid (e.g., a semi-dilute polymer solution or a polymer melt), a suspended conical droplet is formed, whereby the surface tension of the droplet is in equilibrium with the electric field. Electrostatic atomization occurs when the electrostatic field is strong enough to overcome the surface tension of the liquid. The liquid droplet then becomes unstable and a tiny jet is ejected from the surface of the droplet. As it reaches a grounded target, the material can be collected as an interconnected web containing relatively fine, i.e. small diameter, fibers. The resulting films (or membranes) from these small diameter fibers have very large surface area to volume ratios and small pore sizes. However, no practical industrial process has been implemented for electrospinning membranes containing a high percentage of small, e.g., nanosize, fibers. This is because with the production of small fibers, such as nanosize fibers, the total yield of the process is very low and a scale-up process, which maintains the performance characteristics of the films (or membranes), cannot be easily achieved.

U.S. Pat. No. 4,323,525 is directed to a process for the production of tubular products by electrostatically spinning a liquid containing a fiber-forming material. The process involves introducing the liquid into an electric field through a nozzle, under conditions to produce fibers of the fiber-forming material, which tend to be drawn to a charged collector, and collecting the fibers on a charged tubular collector which rotates about its longitudinal axis, to form the fibrous tubular product. It is also disclosed that several nozzles can be used to increase the rate of fiber production. However, there is no suggestion or teaching of how to control the physical characteristics of the tubular product, other than by controlling the charge and rotation speed of the tubular collector. For example, there is no teaching or suggestion of controlling jet formation, jet acceleration or fiber collection for individual jets. It is further noted that the spinning process of the '525 patent is used to fabricate tubular products having a homogenous fiber matrix across the wall thickness.

U.S. Pat. No. 4,689,186 is directed to a process for the production of polyurethane tubular products by electrostatically spinning a fiber-forming liquid containing the polyurethane. It is disclosed that auxiliary electrodes can be placed around the collector to help facilitate collection of the fibers. It is disclosed that the auxiliary electrodes can be arranged to facilitate separation or to prevent adhesion of the formed fibers. There is no teaching or suggestion of independently controlling jet formation, jet acceleration and fiber collection. It is also noted that the spinning process of the '186 patent is used to fabricate tubular products having a homogenous fiber matrix across the wall thickness.

The above mentioned references do not address the problems associated with producing membranes or other articles on an industrial scale, without adversely affecting the performance characteristics of the resulting products.

Thus, there is a need for improved electrospinning methods for producing fibers and membranes on an industrial scale which do not have the above-mentioned disadvantages.

SUMMARY OF INVENTION

According to the present invention, it has now been found that polymeric fibers can be produced by an elecrospinning process having improved control over fiber formation and transportation. In addition, membranes can be produced by electrospinning with the apparatus and according to the methods of the present invention on an industrial scale without the above-mentioned disadvantages.

In one aspect, the invention relates to a method for electrospinning a polymer fiber from a conducting fluid containing a polymer in the presence of a first electric field established between a conducting fluid introduction device and a ground source, which includes modifying the first electric field with a second electric field to form a jet stream of the conducting fluid. The conducting fluid introduction device is preferably a spinneret.

The second electric field can be established by imposing at least one field modifying electrode on the first electrostatic field. The field modifying electrode can be a plate electrode positioned between the conducting fluid introduction device and the ground source.

Preferably, the method includes feeding the conducting fluid to the conducting fluid introduction device at a controlled rate. The rate can be controlled by maintaining the conducting fluid at a constant pressure or constant flow rate.

In one embodiment, the method also involves controlling the electrical field strength at the spinneret tip by adjusting the electric charge on the field modifying electrode to provide a controlled diameter fiber.

In another embodiment, the method includes imposing a plurality of electrical field modifying electrodes to provide a controlled distribution of electrostatic potential between the spinneret and the ground source.

In another aspect, the invention relates to a method for electrospinning a polymer fiber from a conducting fluid containing a polymer in the presence of an electric field established between a spinneret and a ground source, which includes:

a) forming an electrospinning jet stream of the conducting fluid; and

b) electrically controlling the flow characteristics of the jet stream.

The flow characteristics of the jet stream can be electrically controlled by at least one electrode. The flow characteristics of the jet stream can also be electrically controlled by at least one pair of electrostatic quadrupole lenses. Preferably, the flow characteristics of the jet stream are electrically controlled by a plurality of pairs of electrostatic quadropole lenses and, more preferably, by also using an alternating gradient technique.

In one embodiment, the method involves electrically controlling the flow characteristics of the jet stream to provide a controlled pattern over a desired target area. The controlled pattern can be provided by applying a waveform to the potential on at least one pair of electrostatic quadropole lenses.

In yet another aspect, the invention relates to a method for forming a controlled-dimension and controlled-morphology membrane by electrospinning a plurality of polymer fibers from conducting fluid containing a polymer in the presence of an electric field established between a solution introduction device and a ground source, in which the method includes:

a) forming a plurality of electrospinning jet streams of the conducting fluid; and

b) independently controlling the flow characteristics of at least one of the jet streams.

Preferably, the flow characteristics of at least one of the jet streams are electrically controlled by at least one scanning electrode, more preferably, by at least one pair of scanning electrodes.

In one embodiment, the solution introduction device consists of a plurality of electrospinning spinnerets. Preferably, each spinneret produces an individual jet stream of the conducting fluid and, more preferably, the flow characteristics of each individual jet stream can be independently controlled.

Preferably, each spinneret has at least one scanning electrode for electrically controlling the flow characteristics of the individual jet stream. More preferably, each spinneret has two pairs of scanning electrodes for electrically controlling the flow characteristics of the individual jet stream.

It is contemplated that at least two spinnerets can deliver different solutions, wherein different solutions refers to different concentrations of polymer, different polymers, different polymer blends, different additives and/or different solvents.

In another aspect the invention is directed to an electrospinning apparatus for forming a membrane, which includes:

a conducting fluid introduction device for providing a quantity of conducting fluid containing a polymer, the conducting fluid introduction device containing a plurality of electrospinning spinnerets for delivering the conducting fluid, the spinnerets being electrically charged at a first potential;

a ground member positioned adjacent to the spinnerets and electrically charged at a second potential different from the first potential, thereby establishing an electric field between the spinnerets and the ground member;

a support member disposed between the spinnerets and the ground member and movable to receive fibers formed from the conducting fluid; and

means for controlling the flow characteristics of conducting fluid from at least one spinneret independently from the flow characteristics of conducting fluid from another spinneret.

Preferably, the means for independently controlling the flow characteristics includes at least one electrode disposed adjacent each spinneret, each electrode being charged at a potential different from and separate from the first potential.

Preferably, each spinneret has two pairs of scanning electrodes for electrically separately controlling the flow characteristics of conducting fluid from the spinneret.

The means for independently controlling the flow characteristics can include a means for individually electrically turning on and off a respective spinneret. Preferably, the means for individually electrically turning on and off a respective spinneret contains at least one scanning electrode associated with each spinneret.

The means for independently controlling the flow characteristics can also contain a means for applying an alternating gradient to the conducting fluid delivered from the spinnerets. Preferably, the means for applying said alternating gradient includes a plurality of pairs of electrostatic quadropole lenses.

In one embodiment, the electrospinning apparatus includes a probe associated with at least one spinneret, the probe being disposed between the electrode and the ground member, the probe being electrically charged at a potential different from the spinneret and the electrode.

The electrospinning apparatus will preferably contain a pump for supplying conducting fluid to the conducting fluid introduction device at a predetermined pressure. The pump can also be adapted to control the supply rate of conductive fluid at a constant flow rate or at a constant pressure.

The electrospinning apparatus will preferably include a pump system for supplying different conducting fluids to at least two individual spinnerets.

In one embodiment, the conducting fluid introduction device contains a slit-die defining the plurality of spinnerets. The adjacent spinnerets can be interconnected by slits. In such an embodiment, the spinnerets can be defined by openings in the slit-die and the slits interconnecting the spinnerets are of configurations smaller than the openings. The apparatus can also contain a plurality of scanning electrodes disposed adjacent to each of the spinnerets.

In another embodiment, the solution introduction device includes a matrix defining the plurality of spinnerets, the spinnerets being disposed in the matrix in electrical isolation from each other. At least two individual spinnerets can be electrically charged to a different potential. The solution introduction device can also contain a plurality of individual electrodes in which at least one individual electrode is disposed adjacent to each individual spinneret. At least two individual electrodes can be electrically charged to a different potential.

In yet another aspect, the invention is directed to an apparatus for forming a membrane by electrospinning a plurality of polymer fibers from a conducting fluid which contains a polymer in the presence of an electric field between a conducting fluid introduction device and a ground source, in which the apparatus contains an improved conducting fluid introduction device which includes a plurality of spinnerets, each for independently delivering a controlled quantity of conducting fluid at a controlled pressure or flow rate, the spinnerets being charged at an electric potential and being disposed relative to each other to normally interfere with the electric field produced by adjacent spinnerets, each of the spinnerets having a tip at which conducting fluid exits configured to have an electrostatic field strength at each tip stronger than the liquid surface tension at each of the tips.

Each of the tips can be configured by having a tip with a selected geometric profile, a selected spatial relationship relative to other spinneret tips or a combination of both.

The apparatus containing the improved conducting fluid introduction device can also include an electrode associated with each spinneret configured to produce an electrical potential to at least partially screen electric field interference from adjacent spinnerets.

The apparatus containing the improved conducting fluid introduction device can also include a means for at least partially shielding a spinneret from electric field interference from adjacent spinnerets. The means for shielding can be a physical barrier disposed between adjacent spinnerets. The barrier will preferably have a conical shape.

The present invention provides an apparatus and methods for producing fibers and membranes by electrospinning with improved control over fiber formation and transportation. It also provides an apparatus and methods for producing membranes containing nanosize fibers on an industrial scale, without the above-mentioned disadvantages.

Additional objects, advantages and novel features of the invention will be set forth in part in the description and examples which follow, and in part will become apparent to those skilled in the art upon examination of the following, or may be learned by practice of the invention. The objects and advantages of the invention may be realized and attained by means of the instrumentalities and combinations particularly pointed out in the appended claims.

BRIEF DESCRIPTION OF THE FIGURES

FIG. **1** is a schematic of a fluid drop created from a capillary.

FIG. **2** is a schematic of a liquid drop suspended from a capillary.

FIG. **3** is a schematic of a droplet from a single spinneret in an electric field.

FIG. **4** is a schematic of the potential trajectory of a charged fluid jet from a single spinneret.

FIG. **5** is a graph of the electric field strength as a function of distance from the tip of a single spinneret.

FIG. **6** is a schematic of the potential trajectory of charged fluid jets from a multiple spinnerets.

FIG. **7** is a graph of the electric field strength as a function of distance from the tip of a spinneret in a multiple spinneret system.

FIG. **8** is a schematic of an electrospinning system.

FIG. **9** is a schematic of an array of spinnerets for an electrospinning process.

FIG. **10** (*a*) is a side view schematic of a multiple spinneret system for producing membranes in accordance with the invention.

FIG. **10** (*b*) is a cross-sectional view of the spinneret system of FIG. **11** (*a*) as seen along viewing line IV—IV thereof.

FIG. **10** (*c*) is a bottom view of the multiple spinneret system FIG. **11** (*a*).

FIG. **11** is an SEM of a PLA-co-PGA membrane spun from a solution containing 1 wt % KH_2PO_4.

FIG. **12** is an SEM of a PLA-co-PGA membrane spun from a solution without salt added.

FIG. **13** is an SEM of a membrane described in Example 1.

FIG. **14** is an SEM of a PAN membrane described in Example 2.

FIG. **15** is an SEM of a membrane described in Example 4.

FIG. **16** is an SEM of a PLA membrane described in Example 5.

FIG. **17** is an SEM of a dual thickness fiber PLA membrane described in Example 6.

FIG. **18** is an SEM of a copper plated PAN membrane described in Example 10.

DETAILED DESCRIPTION OF THE INVENTION

The present invention is directed to an apparatus and methods for producing polymeric fibers and membranes containing such fibers by electrospinning with improved control over fiber formation and transportation.

The present invention is also directed to an apparatus and methods for producing polymeric membranes by electrospinning a plurality of polymeric fibers simultaneously in a multiple jet system. This allows for high production rates and is necessary for a commercially viable process. However, in order to produce membranes by a multiple jet system, and maintain the desired performance characteristics of the membranes, it is necessary to control the flow characteristics of individual jet streams of the conducting fluid, as discussed more fully below.

By "flow characteristics" (of the conducting fluid) is meant the jet formation and jet acceleration of the conducting fluid which exits from the conducting fluid introduction device, e.g., the spinneret tip, as well as the directional flow of the jet stream in three dimensional space. Thus, controlling the flow characteristics can include controlling jet formation, controlling jet acceleration, directing the jet stream to a desired target in three dimensional space, steering the jet stream to different targets during the spinning process or a combination of these.

Nanofiber Fabrication Technique By Electrospinning

The invention is directed to improved methods and apparatus for electrospinning fibers and membranes from a conducting fluid containing a polymeric material.

The mechanical forces acting on the conducting fluid, which must be overcome by the interaction between an electrostatic field and the conducting fluid to create the electrospinning jet, can be understood by looking at a fluid drop in a capillary tube. For a fluid drop created from a capillary, as shown schematically in FIG. **1**, a higher pressure is developed within the drop due to molecular interactions. This excess pressure Δp inside the drop, which acts upon the capillary cross-section area πr^2, is counterbalanced by the surface tension Y acting on the circumference $2\pi r$, i.e. $\Delta p \cdot \pi r r^2 = Y \cdot 2\pi r$, or

$$\Delta p = \frac{2Y}{r} \tag{1.1}$$

Formula 1.1 reveals that both the drop excess pressure Δp and the surface energy per unit drop volume $(4\pi r^2 Y/[(4\pi/3)r^3])=3Y/r)$ become large when r is small.

The surface tension of a liquid drop hanging from a capillary tip (pendant drop), as shown schematically in FIG. **2**, can be derived from the droplet shape, which is determined by a balance of all the forces acting upon the droplet, including gravity. The droplet surface tension can be related to the droplet shape as follows.

$$Y = g\Delta\rho r_0^2/\beta \tag{1.2}$$

where $\Delta\rho$ is the density difference between fluids at the interface ($\Delta\rho=\rho$ for the droplet having a liquid/air interface), g is the gravitational constant, r_0 is the radius of drop curvature at the apex and β is the shape factor which can be defined by:

$$dx/ds = \cos\phi$$

$$dz/ds = \sin\phi$$

$$d\phi/ds = 2 + \beta z - \sin\phi/x \tag{1.3}$$

Numerical calculation can determine the value of β accurately.

A droplet from a single spinneret in an electrostatic field E, is shown schematically in FIG. **3**. If a liquid has conductivity other than zero, the electric field will cause an initial current flow or charge rearrangement in the liquid. The positive charge will be accumulated at the surface until the net electric field in the liquid becomes zero. This condition is necessary for the current flow to be zero in the liquid. The duration τ of this flow is typically $\tau=\epsilon/\sigma$ where ϵ is the permitivity and σ is the conductivity of the liquid. With a surface charge density (per unit area) ρ_s, the (surface) force F_s exerted on the surface by the electrostatic field E on the droplet per unit area is:

$$F_s = \rho_s(\sigma)E \tag{1.4}$$

The conductivity σ of the liquid can be adjusted, e.g., by adding an ionic salt. Thus, the surface charge density per

unit area can be tuned accordingly. With a sufficiently strong electrostatic field at the tip, the surface tension Y can be overcome, i.e.,

$$F_s=\rho_s(\sigma)E\geq Y-\rho_0 Vg \quad (1.5)$$

with ρ_0, V, and g being the density, the volume of the droplet and the gravitational acceleration, respectively. If this condition is met, the droplet shape will change at the tip to become the "Taylor" cone and a small jet of liquid will be emitted from the droplet. If the electrostatic field remains unchanged, the liquid moving away from the surface of the droplet will have net charges. This net excess charge is directly related to the liquid conductivity. Furthermore, the charged jet can be considered as a current flow, J(σ, E), which will, in turn, affect the electric field distribution on the tip of the droplet, i.e.,

$$E=E_0+E'(J) \quad (1.6)$$

with E_0 being the applied field threshold in the absence of fluid flow. For polymer solutions above the overlap concentration, the evenly distributed charges in the jet repel each other while in flight to the target (ground). Thus the polymer chains are continuously being "stretched" in flight until the stretch force is balanced by the chain restoring force or the chains are landed on the target, whichever comes first.

In the electrospinning process according to the invention, a key requirement is to maintain the droplet shape. This requirement involves control of many parameters including liquid flow rate, electric and mechanical properties of the liquid, and the electrostatic field strength at the tip. In order to achieve high field strengths, the curvature of the electrode at the tip has to be sharp (small radius R_0). However, since a stable pendant droplet is controlled by the shape factor β, the curvature r_0 and thus R_0 could not be too small. FIG. **4** shows, as an example, estimates of equal potential lines of a single electrode configuration with a set of specific geometric parameters and the force line for a charge particle in the trajectory that is normal to the equal potential lines. FIG. **5** shows the estimated electric field strength along the jet direction from the tip of the electrode to the ground (plate).

Sub-micron diameter fibers can be produced in accordance with the invention at a relatively high yield. For example, a 40% polymer solution being spun from a spinneret with a diameter of 700 microns, which results in a final filament having a diameter of 250 nm, will have a draw ratio of 7.84×10^6. If the extrudate (conducting fluid) has a rate of about 20 μl/min, the final filament speed will be about 136 m/s, which is a relatively high spinning rate. Thus, a commercially viable process for making membranes according to the invention is achievable with a sufficient number of spinnerets operating at such speeds. For example, if a single jet is capable of processing a 40 wt % polymer solution at a rate of 20 μl/min (i.e. 8 mg/min), then a production unit of 100 jets can produce about 500 g of a membrane in 12 hours of operation. As the average membrane density is about 0.25 g/cm^3 and the average membrane thickness is about 25 microns, about 160 sheets of a membrane (with dimensions of 20×25 cm^2) can be produced per day.

The conducting fluid will preferably include a solution of the polymer materials described more fully below. The polymer material used to form the membrane is first dissolved in a solvent. The solvent can be any solvent which is capable of dissolving the polymer and providing a conducting fluid capable of being electrospun. Typical solvents include a solvent selected from N,N-Dimethyl formamide (DMF), tetrahydrofuran (THF), methylene chloride, dioxane, ethanol, chloroform, water or mixtures of these solvents.

The conducting fluid can optionally contain a salt which creates an excess charge effect to facilitate the electrospinning process. Examples of suitable salts include NaCl, KH_2PO_4, K_2HPO_4, KIO_3, KCl, $MgSO_4$, $MgCl_2$, $NaHCO_3$, $CaCl_2$ or mixtures of these salts.

The polymer solution forming the conducting fluid will preferably have a polymer concentration in the range of about 1 to about 80 wt %, more preferably about 10 to about 60 wt %. The conducting fluid will preferably have a viscosity in the range of about 50 to about 2000 mPa·s, more preferably about 200 to about 700 mPa·s.

The electric field created in the electrospinning process will preferably be in the range of about 5 to about 100 kilovolts (kV), more preferably about 10 to about 50 kV. The feed rate of the conducting fluid to the spinneret (or electrode) will preferably be in the range of about 0.1 to about 1000 microliters/min, more preferably about 1 to about 250 microliters/min.

Preferably the electospinning process includes multiple jets. This allows for the production of membranes containing small diameter fibers in very high yield, making it useful for production on an industrial scale. However, there are constraints associated with trying to use multiple jets in an electrospinning process.

For a configuration with multiple jets, two main factors are to be considered: 1) the liquids should be delivered, either at constant pressure or constant flow rate, to each separate spinneret; and 2) the electrostatic field strength at each tip of the electrode should be strong enough to overcome the liquid surface tension at that tip. The first factor has been resolved by careful mechanical design for controlled solution distribution to each of the spinnerets. With electrodes being placed close to one another, the electrostatic field distribution is changed and the field strength at tip is normally weakened because of the interference from nearby electrodes, i.e.,

$$E_i = E_i^0 + \sum_{j\neq i} E_{ij} + \sum_j E'_{ij}(J_j) \quad (1.7)$$

where E_i^0 is the unperturbed electric field strength due to the single electrode i. E_{ij} is the electric field at location i contributed by electrode j, and $E'_{ij}(J_j)$ is the interference electric field caused by the current J of jet j. FIG. **6** shows the equal potential line of a double jet configuration with the electrodes having the geometrical parameters as that of a single jet.

By following Equation (1.5) for a single jet, the criteria for the multiple jet operation are that, in addition to Equation (1.7), each jet (i) has to meet the following condition:

$$\rho_s^i(\sigma_i)E_i\geq Y_i-\rho_0{}^iV_ig \quad (1.8)$$

Both conditions for Equations (1.7) and (1.8) should be met for multiple jet operation. The multiple jet apparatus of the present invention was based on these two criteria. For example, FIG. **7** shows the estimated electric field strength along the direction from the tip to the ground. In comparison with FIG. **5**, the field strength is less in absolute value. A separate calculation could show that in order to achieve the same field strength as the original unperturbed single jet, the electric potential has to increase from 5.0 kV to 5.6 kV. This demonstrates that the electric field strength for multiple jets can be calculated by using Equation (1.7). Furthermore, a shielding system or a specially shaped electrode to produce a different electric potential may be used to partially screen out the interference from nearby electrodes, making the

scale up operation practical. Numerical estimates, including jet effects based on Equation (1.7), can be used to guide and to obtain an optimal design for specific operations.

With multiple jets, as the electrodes are placed close to one another, the electrostatic field distribution is changed and the field strength of the spinneret i at the tip is altered by the presence of nearby electrodes. The net field strength at the tip i can be represented by three combinations: (1) the unperturbed electric field strength due to the single electrode i, (2) the sum of the electric field strength at location i due to all other electrodes, and (3) the electric field strength at location i generated by all jets (including i). This net field strength at tip i (Ei) can then be used to set the criteria for electrospinning, i.e., the product of surface charge density of the conducting fluid at tip i (S_i) times E_i together with the gravity effect should overcome the surface tension of the field at tip i. These rules represent the fundamental criteria for efficient multiple jet operation and permit optimal design for specific operations that involve multiple parameter adjustments.

In accordance with the present invention, different approaches have been developed to provide for efficient multiple jet operation. These approaches include improvements in the multiple jet electrospinning apparatus to provide sufficient field strength to overcome the surface tension of the conducting fluid and the electric field interference from adjacent spinnerets and jet streams. For example, a spinneret tip configuration can be provided to allow for efficient multiple jet spinning. The spinneret tip configuration can include a selected geometric profile to provide a controlled charge distribution in the conducting fluid at the spirmeret tip as discussed above. The spinneret tip configuration can also include a selected spatial relationship for the spinneret tips relative to each other. For example, the distance from individual spinneret tips to the ground source can be varied, depending upon the relative distance between adjacent spinnerets, to provide more efficient multiple jet spinning.

Another example of an improved electrospinning apparatus is to provide an electrode associated with each spinneret configured to produce an electrical potential to at least partially screen electric field interference from adjacent spinnerets. Another example includes providing a means for at least partially shielding the electric field interference, such as a physical barrier disposed between adjacent spinnerets.

A particular apparatus for producing membranes according to the present invention, which uses a multiple jet electrospinning system, is shown schematically in FIG. **8**. Equipment not essential to the understanding of the invention such as heat exchangers, pumps and compressors and the like are not shown.

Referring now to FIG. **8**, the conducting fluid, which contains the polymer, is supplied by a micro-flow pump system **1**. The conducting fluid preferably contains a polymer, a solvent and a salt, e.g., 25 wt % PLA-DMF solution with 1 wt % KH_2PO_4. The pump system **1** is linked to a computer **2** which controls the flow rate of the conducting fluid by controlling pressure or flow rate. Optionally, different flow rates can be provided and controlled to selected spinnerets. The flow rate will change depending upon the speed of the support membrane **3** and the desired physical characteristics of the membrane, i.e., membrane thickness, fiber diameter, pore size, membrane density, etc.

The pump system **1** feeds the conducting fluid to a multiple jet system **4** that contains manifolds **5** having a bank of spinnerets **6**. The spinnerets each have a tip geometry which allows for stable jet formation and transportation, without interference from adjacent spinnerets or jet streams. A charge in the range of about 20 to about 50 kV is applied to the spinnerets by a high voltage power supply **7**. A hood **8** is positioned over the multiple jet system **4** to remove the solvent at a controlled evaporation rate.

A ground plate **9** is positioned below the multiple jet system **4** such that an electric field is created between the charged spinnerets **6** and the ground plate **9**. The electric field causes tiny jets of the conducting fluid to be ejected from the spinnerets and spray towards the ground plate **9**, forming small, e.g. sub-micron, diameter filaments or fibers.

A moving support membrane **3** is positioned between the charged spinnerets **6** and the ground plate **9** to collect the fibers which are formed from the spinnerets and to from an interconnected web of the fibers. The support membrane **3** moves in the direction from the unwind roll **10** to the rewind roll **11**.

The micro-flow control/pumping system is electrically isolated from the ground and is powered by an isolation transformer **12**.

The post-spinning processors **13** have the functions of drying, annealing, membrane transfer (for example, from a stainless mesh substrate to another substrate, e.g., a Malox mesh) and post-conditioning.

Post-conditioning can include additional processing steps to change the physical characteristics of the membrane itself, e.g., post-curing, or to modify the membrane by incorporating other materials to change the properties of the resulting membrane, e.g., solution coating, spin casting or metal/metal oxide plating the membrane.

Multiple jets with designed array patterns can be used to ensure the fabrication of uniform thickness of the membrane. Hood, heating and sample treatment chambers can also be included to control the solvent evaporation rate and to enhance the mechanical properties. The recovered thickness can be precisely controlled from tens of microns to hundreds of microns. Additional embodiments or modifications to the electrospinning process and apparatus are described below.

Variation of Electric/mechanical Properties of Conducting Fluid

The properties of the resulting membrane produced by electrospinning will be affected by the electric and mechancial properties of the conducting fluid. The conductivity of the macromolecular solution can be drastically changed by adding ionic inorganic/organic compounds. The magnetohydrodynamic properties of the fluid depend on a combination of physical and mechanical properties, (e.g., surface tension, viscosity and viscoelastic behavior of the fluid) and electrical properties (e.g., charge density and polarizability of the fluid). For example, by adding a surfactant to the polymer solution, the fluid surface tension can be reduced, so that the electrostatic fields can influence the jet shape and the jet flow over a wider range of conditions. By coupling a pump system that can control the flow rate either at constant pressure or at constant flow rate, the effect of viscosity of the conducting fluid can be alleviated.

Electrode Design

In another embodiment for producing membranes according to the present invention, the jet formation process during electrospinning is further refined to provide better control over fiber size. Instead of merely providing a charged spinneret and a ground plate, as discussed above, a positively charged spinneret is still responsible for the formation of the polymer solution droplet and a plate electrode with a small exit hole in the center is responsible for the formation of the jet stream. This exit hole will provide the means to let

the jet stream pass through the plate electrode. Thus, if the polymer droplet on the positively charged spinneret has a typical dimension of 2–3 mm and the plate electrode is placed at a distance of about 10 mm from the spinneret, a reasonable electrostatic potential can be developed. The short distance between the two electrodes implies that the electrostatic potential could be fairly low. However, the resultant electric field strength could be sufficiently strong for the electrospinning process. By varying the electric potential of the spinneret, the jet formation can be controlled and adjusted. Such an electrode configuration should greatly reduce the required applied potential on the spinneret from typically about 15 kilovolts (kV) down to typically about 1.5 to 2 kV (relative to the ground plate potential). The exact spinneret potential required for stable jet formation will depend on the electric/mechanical properties of the specific conducting fluid.

Control of Jet Acceleration and Transportation

In another preferred embodiment for producing membranes according to the present invention, the jet stream flight is also precisely controlled. The jet stream passing through the plate electrode exit hole is positively charged. Although this stream has a tendency to straightening itself during flight, without external electric field confinement the jet will soon become unstable in its trajectory. In other words, the charged stream becomes defocused, resulting in loss of control over the microscopic and macroscopic properties of the fluid. This instability can be removed by using a carefully designed probe electrode immediately after the plate electrode and a series of (equally) spaced plate electrodes. The electrode assembly (or composite electrode), i.e., the probe electrode and the plate electrodes, can create a uniform distribution of electrostatic potential along the (straight) flight path. The acceleration potential is formed by placing the base potential of the spinneret at about +20 to +30 kV above the target (at ground potential) while the electrostatic potential of the probe electrode can be adjusted to slightly below the plate electrode base potential. The composite electrodes are capable of delivering the jet stream to a desired target area. The composite electrode can also be utilized to manipulate the jet stream. By changing the electrostatic potential, the jet stream acceleration is altered, resulting in varying the diameter of the formed nano-fiber. This electrostatic potential variation changes the jet stream stability, and therefore, corresponding changes in the composite electrode can be used to stabilize the new jet stream. Such a procedure can be used to fine-tune and to change the fiber diameter during the electrospinning process.

Jet Manipulation

In yet another embodiment, the jet stream can be focused by using an "Alternating Gradient" (AG) technique, widely used in the accelerator technology of high-energy physics. The basic idea is to use two pairs of electrostatic quadrupole lenses. The second lens has the same geometric arrangement as the first lens with a reversed (alternate) electric gradient. The positively charged jet stream will be focused, for example, in the xz plane after the first lens and then be refocused in the yz plane after the second lens. It is noted that the z-direction represents the direction of the initial flight path. By applying an additional triangle-shaped waveform to the potential on one of the pairs of the quadrupole, the jet can be swept across the target area, allowing the control of the direction of the jet stream. Furthermore, with varying waveform of the 'sweep' potential, a desired pattern on the target can be formed.

Pattern Design by Electrospinning

In yet another embodiment for producing membranes according to the present invention, reference will be made to FIG. **9**. In this embodiment, the conducting fluid is introduced into the electrospinning process through an array of electrospinning spinnerets **20**. The array of electrospinning spinnerets are assembled in a matrix **21** that provides electrical isolation for the spinnerets, with each spinneret having two pairs (X and Y direction) of miniature scanning electrodes **22**. The spinneret **20** and the scanning electrodes **22** are electrically wired such that each individual polymer solution jet can be turned on and off and be steered to a finite size target area. As each spinneret **20** can be turned on/off independently by electricity, the response time will be relatively fast. Also, each spinneret **20** can deliver a different solution, e.g., each containing a different drug or concentration. A designed pattern can be obtained in the resultant membrane. This pattern can be precisely controlled by a computer and can be tailored for specific medical applications.

Multiple Jet Slit-Die Geometry

In yet a further embodiment for producing membranes in accordance with the present invention, reference is made to FIGS. **10**(*a*)–**10**(*c*). In this embodiment, a multiple jet system **30** comprises an array of electrospinning spinnerets **31**, each spinneret **31** being defined by a slit **32** formed in a slit-die **33** that is coupled to high voltage to serve as an electrode disposed above the ground plate **34**. As shown in detail in FIG. **10**(*c*), the spinnerets **31** are each interconnected by selectively narrow slits **35**, such that each spinneret **31** is interconnected to a neighboring spinneret **31** by a slit **35**. The conducting fluid will not flow through the slits **35**, but will flow through each of the spinnerets **31** in a more robust manner.

The slit-die approach permits three distinct advantages that are not available by using individual spinnerets. First, the slit-die is made up of two separate components with controlled dimensions of the effective openings for the spinnerets. In other words, by changing the distance between the two components, the effective openings of the spinnerets become available. Second, the presence of slits between the larger openings permits fluid flow and thereby equalizes the pressure difference between the spinnerets. Third, the presence of slits can also reduce potential blockage of the fluid.

The membranes produced by the slit-die approach can achieve a larger degree of flexibility in the structures. For example, different size nanofibers can be produced from the same slit-die setup.

Control of Degradation Rate through Processing Parameters

As discussed above, very different fiber diameter and morphology in the membrane can be obtained by changing the parameters in the electrospinning process. As the degradation rate is inversely proportional to the fiber diameter, the manipulation capability through processing parameters provides not only the means to control the degradation rate of the membrane but also the ways to control drug loading efficiency and the drug release rate.

For example, it is believed that a change in charge density (through the addition of salts) can significantly affect the fiber diameter. When 1 wt % potassium phosphate (KH_2PO_4) was added to a PLA-co-PGA solution, the fiber diameter became much thinner (see SEM picture in FIG. **11**) than the one with no salt added (FIG. **12**). Thus, it is believed that higher excess charge density generally favors the production of thinner fibers and lower excess charge density favors the production of thicker fibers. Several other kinds of salts (e.g. NaCl, KH_2PO_4, KIO and K_3PO_4), which are all biologically compatible to the body, are also contemplated.

The apparatus and methods according to the invention can be used for electrospinning any fiberizable material.

Examples of such materials include polymers, such as PLA, PGA, PEO, nylon, polyesters, polyamides, poly(amic acids), polyimides, polyethers, polyketones, polyurethanes, polycaprolactones, polyacrylonitriles and polyaramides.

The fiberizable material is preferably a biodegradable or bioabsorbable polymer, when it is desired to produce membranes for medical applications. Examples of suitable polymers can be found in Bezwada, Rao S. et al. (1997)*Poly(p-Dioxanone) and its copolymers, in Handbook of Biodegradable Polymers*, A. J. Domb, J. Kost and D. M. Wiseman, editors, Hardwood Academic Publishers, The Netherlands, pp. 29–61, the disclosure of which is incorporated herein by reference in its entirety.

In an embodiment for preparing membranes useful in medical applications the polymer is a biodegradable and/or bioabsorbable polymer which contains a monomer selected from the group consisting of a glycolid, lactide, dioxanone, caprolactone and trimethylene carbonate. By the terminology "contains a monomer" is intended a polymer which is produced from the specified monomer(s) or contains the specified monomeric unit(s). The polymer can be a homopolymer, random or block co-polymer or heteropolymer containing any combination of these monomers. The material can be a random copolymer, block copolymer or blend of homopolymers, copolymers, and/or heteropolymers that contains these monomers.

In one embodiment, the biodegradable and/or bioabsorbable polymer contains bioabsorbable and biodegradable linear aliphatic polyesters such as polyglycolide (PGA) and its random copolymer poly(glycolide-co-lactide) (PGA-co-PLA). The FDA has approved these polymers for use in surgical applications, including medical sutures. An advantage of these synthetic absorbable materials is their degradability by simple hydrolysis of the ester backbone in aqueous environments, such as body fluids. The degradation products are ultimately metabolized to carbon dioxide and water or can be excreted via the kidney. These polymers are very different from cellulose based materials, which cannot be absorbed by the body.

Other examples of suitable biocompatible polymers are polyhydroxyalkyl methacrylates including ethylmethacrylate, and hydrogels such as polyvinylpyrrolidone, polyacrylamides, etc. Other suitable bioabsorbable materials are biopolymers which include collagen, gelatin, alginic acid, chitin, chitosan, fibrin, hyaluronic acid, dextran and polyamino acids. Any combination, copolymer, polymer or blend thereof of the above examples is contemplated for use according to the present invention. Such bioabsorbable materials may be prepared by known methods.

Particularly useful biodegradable polymers include polylactides, poly-glycolides, polycarprolactone, polydioxane and their random and block copolymers. Examples of specific polymers include poly D, L-lactide, polylactide-co-glycolide (85:15) and polylactide-co-glycolide (75:25).

Preferably, the biodegradable polymers discussed above will have a molecular weight in the range of about 1,000 to about 1,000,000 g/mole, more preferably about 4,000 to about 250,000 g/mole. Blends of different molecular weight polymers are also contemplated. A small percentage of a low molar mass monomer can also be added to the higher molar mass polymer.

The methods and apparatus according to the invention are capable of producing membranes containing fibers having diameters in the range from about 10 up to about 1,000 nanometers, more preferably about 20 to about 500 nanometers.

It is also possible to produce membranes containing fibers having different diameters with a controlled percentage of sub-micron diameter fibers. Preferably, the membrane will contain at least about 10 wt % of sub-micron diameter fibers, more preferably at least about 80 wt %.

Membrane can also be produced containing fibers of different materials, e.g., different biodegradable and bioabsorable polymers.

Optionally, additives, e.g., one or more medicinal agents, can be incorporated into the fibers produced in accordance with the invention. The additives can be mixed with the fiberizable material, e.g., polymer, prior to formation of the fibers.

The chemical composition, i.e., specific polymers or blends of polymers, the fiber diameter, the membrane morphology and the porosity of the non-woven membrane can be controlled to provide selectable performance criteria for the membranes being produced. The membrane can also contain a plurality of fibers which have different medicinal agents or different concentrations of medicinal agents. Such membranes offer unique treatment options with combinations of medicinal agents and release profiles.

In one embodiment, the methods of the invention can provide a plurality of different layers. The layers can have the same or different chemical composition, fiber diameters, membrane morphology and porosity.

In such an embodiment, it is also contemplated that additives can be incorporated between the layers of the multi-layered membrane, instead of or in addition to, incorporating additives into the fiber structure itself.

Membranes can be prepared for use in applications where the membrane contains a high percentage of very small diameter fibers or where relatively high surface area to structure is desired. As a consequence of preparing membranes using the present invention, the structure of the membrane can be tailored to contain a highly controlled amount of very small diameter fibrils or to exhibit an increased surface area over similar membraneous structures prepared without the present invention. Moreover, the desired characteristics of the membranes can be maintained while producing the membranes at a rate higher than without the present invention.

Examples of membranes which exhibit the above described characteristics that can be produced according to the invention include medical devices or articles, such as drug delivery devices, adhesion-reducing barriers, scaffolding for guided tissue regeneration, anti-fibroblastic growth barriers, or nerve coaptation wraps, as well as non-medical devices or articles, such as separator membranes or current collectors useful in batteries or fuel cells. Further examples are described in co-pending, commonly owned patent application Ser. No. 09/859,007, entitled "Biodegradable and/or Bioabsorbable Fibrous Articles and Methods For Using The Articles For Medical Applications," filed on even date herewith.

EXAMPLES

The following non-limiting examples have been carried out to illustrate preferred embodiments of the invention. These examples include the preparation of membranes according to the invention, analysis of the membranes and testing of the membranes.

Example 1

A membrane according to the invention was prepared as follows: a 30 wt % PLG copolymer/DMF solution was

prepared by slowly dissolving PLG copolymer pellets (inherent viscosity of 0.55–0.75. Birmingham Polymers Inc., AL) into an N,N-dimethyl formamide (DMF) solvent at room temperature. The solution was then loaded into the 5 ml syringe fitted with a gauge 20 needle, and delivered through a Teflon tube (0.03" ID) to the exit hole of an electrode having a diameter of 0.025". The solution was pumped and controlled by a syringe pump (Harvard Apparatus "44" series, MA) at a flow rate of 20 microliters/min. A 25 kV positive high voltage (by Glassman High Voltage Inc.) was applied on the electrode. The distance from the tip of the electrode to the grounded collecting plate was 15 cm. A tiny electrospinning jet was formed and stabilized in 30 seconds under these conditions. The collecting plate was movable and controlled by a stepper motor. The collecting plate was continually moved at a rate of 1 mm/sec until a membrane having a relatively uniform thickness of about 100 microns was obtained. An SEM (Scanning Electron Microscopy) image of the membrane is shown in FIG. **13**.

Example 2

A membrane according to the present invention, fabricated by a multi-jet electrospinning process, was prepared as follows: an 8 wt % polyacrylonitrile (PAN) (Aldrich Chemical Company, Inc.)/DMF solution was prepared by slowly adding and dissolving the polymer powders into an organic solvent, which was DMF (N,N-dimethyl formamide), at room temperature. After the solution was completely mixed, it was then loaded into 6 individual syringes, each with a volume of 5 mL. The syringes were fitted with gauge 20 needles and the solution was delivered through Teflon tubes (0.03" ID) to 6 electrodes, each having a tiny hole with a diameter of 0.025". The geometry of the electrodes was designed in such a way so that the largest electric field strength could be achieved at the tip of the electrode under a given electric potential, which included a hemispherical tip with a radius of 0.125 inch and a central hole of 0.025 inch diameter. The polymer solution was finally pumped and controlled by a syringe pump (Harvard Apparatus "44" series, MA) at a flow rate of 25 microliters/min. In addition, a 26 kV positive high voltage (by Glassman High Voltage Inc.) was applied on the electrodes in order to obtain the existence of six well-stabilized electrospinning jets. The distance from the tip of the electrodes to the grounded collecting plate was 15 cm and the tip of the electrodes were 2 cm apart from each other. The collecting plate was movable and controlled by a step motor. The collecting plate was continually moved at a rate of 1 mm/sec until a bioabsorable and biodegradable PAN membrane having a relatively uniform thickness of about 100 microns was obtained. An SEM (Scanning Election Microscopy) image for the PAN membrane is shown in FIG. **14**.

Example 3

A polymer solution suitable for electrospinning, which contained a drug, was prepared as follows: A sample of Poly(DL-lactide) ("PLA") purchased from Birmingham Polymers, Inc., Birmingham, Ala. (Product No. D98120) having a weight average molecular weight of 1.09×10^5 g/mole and a polydispersity of 1.42 was stored in a vacuum oven at room temperature. The pellets were dissolved in DMF purchased from Fisher Scientific, Fair lawn, N.J. to form a 25 wt % solution. The antibiotic drug used was Mefoxin™ from Merck & Co., Inc., West Point, Pa. The antibiotic was dissolved in distilled water and then mixed with PLA/DMF solution in appropriate amounts to form the solution with a PLA/drug ratio of 9:1. A stable jet was formed using this solution in the electrospinning process described in Example 1.

Example 4

A second membrane was prepared in a similar manner to Example 1, except that a drug solution was added to the polymer solution prior to electrospinning and the voltage applied to the electrode was adjusted. The drug solution was prepared by dissolving 0.6 grams of Mefoxin (Merck & Co Inc.) into 0.4 grams of water. The drug solution was then very slowly (dropwise) added to the polymer solution with gentle stirring until it reached a final PLG/drug ratio of 19:1. A 20 kV positive high voltage (by Glassman High Voltage Inc.) was applied on the electrode. All other parameters were the same as Example 1. An SEM (Scanning Electron Microscopy) image of the membrane containing the drug is shown in FIG. **15**.

Example 5

A membrane was fabricated as follows: A 35 wt % PLA polymer/DMF solution was prepared by slowly dissolving the PLA pellets. The solution was fed through the syringe pump system to the electrodes at a flow rate of 20 microliter/min per jet. A 25 kV positive high voltage was applied to the electrode. FIG. **16** shows a typical scanning electron microscopy (SEM) image of an electrospun PLA membrane made by the procedures described above. It has an average fiber diameter of 200 nm. The typical membrane density is about 0.25 g/cm^3, as compared to the neat resin (PLA) density of 1.3 g/cm^3.

Example 6

A membrane containing dual thickness fibers was prepared as follows: a 25 wt % PLA-DMF solution was prepared by slowly dissolving PLA polymer pellets having the same molecular weight and poly dispersity as in Example 2 into a DMF solvent. The drug solution was then very slowly (dropwise) added to the polymer solution with gentle stirring until it reached a final PLG/drug ratio of 19:1. A 20 kV positive high voltage (by Glassman High Voltage Inc.) was applied on the electrode. All other parameters were the same as Example 1. A membrane having a network structure consisting of large size filaments (2 micron diameter), very fine fibrils (50 nanometer diameter) and small blobs was obtained by varying solution feeding speed ranging from 20 μl/min to 70 μl/min. An SEM of the resulting membrane is shown in FIG. **17**.

Example 7

A biodegradable and bioabsorbable composite membrane consisting of two polymer components of different hydrophobicity according to the present invention was prepared as follows: First, a 6 wt % polyethylene oxide (PEO)/DMF solution was prepared by slowly adding the polymer powders into an organic solvent, which was DMF (N,N-dimethyl formamide). Second, a 30 wt % polylactide glycolide (PLG)/DMF solution was made by dissolving the polymers into DMF as well. After these two solutions were each completely homogenized at the room temperature, they were then loaded separately into two individual syringes, each with a volume of 5 mL. Next, the syringes were fitted with 2 gauge 20 needles and delivered through Teflon tubes to the electrodes, each having a tiny hole with a diameter of 0.025". The polymer solutions were finally pumped and

controlled by a syringe pump at a flow rate of 20 microliters/min. In addition, a 25 kV positive high voltage was applied on two separate electrodes in order to obtain the existence of well-stabilized electrospinning jets. The distance from the tips of the electrodes to the ground collecting plate was 15 cm. Furthermore, a step motor was utilized in order to control the movement of the ground collector so that it was capable to move in different directions, either left or right. The collecting plate was moving at a rate of 5 steps/sec continuously until a biodegradable and bioabsorable membrane having a relatively uniform thickness of 100 microns was achieved.

Example 8

A biodegradable and bioabsorbable composite membrane consisting of two component polymer blend of different hydrophobicity according to the present invention was prepared as follows: First, a 2 wt % polyethylene oxide (PEO, Mw=100,000 g/mol)/DMF solution was prepared by slowly adding the polymer powders into an organic solvent, which was DMF (N,N-dimethyl formamide). Second, a 20 wt % polylactide glycolide (PLG)/DMF solution was made by dissolving the polymers into DMF as well. These two solutions were mixed together and were each completely homogenized at the room temperature. They were then loaded separately into two individual syringes, each with a volume of 5 mL. Next, the syringes were fitted with 2 gauge 20 needles and delivered through Teflon tubes to the electrodes, each having a tiny hole with a diameter of 0.025". The polymer solutions were finally pumped and controlled by a syringe pump at a flow rate of 20 microliters/min. In addition, a 25 kV positive high voltage was applied on two separate electrodes in order to obtain the existence of well-stabilized electrospinning jets. The distance from the tips of the electrodes to the ground collecting plate was 15 cm. Furthermore, a step motor was utilized in order to control the movement of the ground collector so that it was capable to move in different directions, either left or right. The collecting plate was moving at a rate of 5 steps/sec continuously until a biodegadable and bioabsorable membrane having a relatively uniform thickness of 100 microns was achieved.

Example 9

A polyimide membrane was prepared according to the present invention as follows: First, a solution was prepared by slowly dissolving pyrromelletic dianhydride (PMDA) and oxydianiline (ODA) in N,N-dimethylacetamide (DMAc) to provide a solution containing 10 wt % PMDA and 10 wt % ODA. The resulting solution was then reacted under condensation reaction conditions at a temperature of 50° C. for 30 minutes to provide a solution of poly(amic acid) pre-polymers. The yield was controlled to about 50% to avoid cross linking. The filtered and recovered poly(amic acid) solution contained about 10 wt % of solute. After the poly(amic acid) solution was completely homogenized at the room temperature, it was then loaded into a 5 ml syringe fitted with a gauge 20 needle and delivered through Teflon tubes to an electrode having a tiny hole with a diameter of 0.025". The pre-polymer solution was pumped and controlled by a syringe pump at a flow rate of 20 microliters/min. A 25 kV positive high voltage was applied on the electrode in order to obtain the existence of a well-stabilized electrospinning jet. The distance from the tip of the electrode to the ground collecting plate was 15 cm. A step motor was utilized in order to control the movement of the ground collector so that it was capable to move in different directions, either left or right. The collecting plate was moving at a rate of 1 mm/sec continuously until a poly(amic acid) membrane having a relatively uniform thickness of 100 microns was achieved.

The poly(amic acid) membrane then subjected to a post-curing step to convert the membrane to a polyimide membrane. In the post-curing step, the poly(amic acid) membrane was imidized by thermal conversion by maintaining the membrane at about 250° C. under a vacuum for 120 minutes. The resulting membrane was yellowish with a silky tissue-paper like texture and had excellent environmental stability.

Example 10

Membranes useful as a separators or current collectors for a battery or fuel cell were prepared by subjecting a PAN membrane (prepared according to Example 2) and a polyimide membrane (prepared according to Example 9) each to a post-conditioning step in which a conductive layer was applied to the surface of each of the membranes. Since the membranes were not electrically conductive, they were plated with a thin layer of metal (e.g. copper) to induce conductivity using an electroless plating procedure. Electroless plating refers to the autocatalytic or chemical reduction of aqueous metal ions plated to a base substrate. This technique has been routinely used for coating of an object (such as a plastic part) as a pretreatment step. Unlike conventional electroplating, no electrical current is required for deposition. Components of the electroless bath typically include an aqueous solution of metal ions, catalyst, reducing agent(s), complex agent(s) and bath stabilizer(s). In electroless plating, the substrate being plated must be catalytic in nature (usually induced by surface pre-treatment) and can induce the autocatalytic reaction in the bath to continuously deposit the metal. The metal ions are reduced to metal by the action of the reducing agents.

The following electroless plating procedure was used to coat the membranes with copper: In a first step, each membrane was immersed in an acidic aqueous solution of stannous chloride ($SnCl_2$) (0.06 g $SnCl_2$ in 20 ml H_2O) kept at 45° C. for 30 minutes. In a second step, each of the recovered membranes from step **1** were immersed in a palladium chloride ($PdCl_2$) solution (having a concentration of 1 mg/ml of H_2O) at 70° C. for 60 minutes. An electroless copper bath was prepared by combining 15 g/liter of copper sulfide (metal salt), 40 g/liter of Rochelle salt (complexing agent), 6 ml/liter of 37% formaldehyde (reducing agent) and 0.01 g/liter of vanadium oxide (stabilizer). The pH level of the bath was kept at about 12 and the bath temperature at 70–75° C. Each membrane recovered from step **2** was immersed in the electroless copper bath for 30 minutes. The plating rate of this bath was about 1 to 5 μm/hr, with a target layer thickness of less than 100 microns. As the fiber surface to volume ratio is extraordinarily high and the fiber diameter is small, the plating process did not cover the entire contour of the membrane surface evenly. However, with plating of a large fraction of the membrane surface to the desired thickness, the resulting membrane exhibited sufficient electric conductivity for battery and fuel cell applications as separator membranes and current collectors. An SEM of the resulting copper plated PAN membrane is shown in FIG. **18**.

Thus, while there has been disclosed what is presently believed to be preferred embodiments of the invention, those skilled in the art will appreciate that other and further changes and modifications can be made without departing

from the scope or spirit of the invention, and it is intended that all such other changes and modifications are included in and are within the scope of the invention as described in the appended claims.

We claim:

1. A method for electrospinning a polymer fiber from a conducting fluid containing said polymer in the presence of a first electric field established between a conducting fluid introduction device and a ground source comprising:

modifying said first electric field with a second electric field to form a jet stream of said conducting fluid and forming a polymer fiber.

2. A method according to claim 1, wherein said conducting fluid introduction device is a spinneret.

3. A method according to claim 1, wherein said second electric field is established by imposing at least one field modifying electrode.

4. A method according to claim 3, wherein said field modifying electrode is a plate electrode positioned between said conducting fluid introduction device and said ground source.

5. A method according to claim 3, further comprising controlling the electrical potential on the conducting fluid introduction device by adjusting the electric charge on said field modifying electrode.

6. A method according to claim 3, further comprising imposing a plurality of electrical field modifying electrodes, to provide a controlled distribution of electrostatic potential along the direction of flow of said jet stream.

7. A method according to claim 1, further comprising feeding said conducting fluid to said conducting fluid introduction device at a controlled rate.

8. A method according to claim 7, wherein said rate is controlled by maintaining said conducting fluid at a constant pressure or constant flow rate.

9. A method for electrospinning a polymer fiber from a conducting fluid containing a polymer in the presence of an electric field established between a spinneret and a ground source comprising:

a) forming an electrospinning jet stream of said conducting fluid; and

b) electrically controlling the flow characteristics of said jet stream to provide a controlled pattern over a desired target area; and

c) forming a polymer fiber from said jet stream.

10. A method according to claim 9, wherein said flow characteristics of said jet stream are electrically controlled by at least one electrode.

11. A method according to claim 9, wherein said flow characteristics of said jet stream are electrically controlled by at least one pair of electrostatic quadrupole lenses.

12. A method according to claim 11, wherein said flow characteristics of said jet stream are electrically controlled by a plurality of pairs of electrostatic quadropole lenses.

13. A method according to claim 12, wherein said flow characteristics of said jet stream are electrically controlled by using an alternating gradient technique.

14. A method according to claim 9, wherein said controlled pattern is provided by applying a waveform to the potential on at least one pair of electrostatic quadropole lenses.

15. A method for forming a controlled-dimension and controlled-morphology membrane by electrospinning a plurality of polymer fibers from a conducting fluid containing said polymer in the presence of an electric field established between a solution introduction device and a ground source, said method comprising:

a) forming a plurality of electrospinniflg jet streams of said conducting fluid;

b) independently controlling the flow characteristics of at least one of said jet streams; and

c) forming a membrane.

16. A method according to claim 15, wherein said flow characteristics of at least one of said jet streams are controlled by at least one scanning electrode.

17. A method according to claim 15, wherein said flow characteristics of at least one or more of said jet streams are controlled by at least one pair of scanning electrodes.

18. A method according to claim 15, wherein said solution introduction device consists of a plurality of electrospinning spinnerets.

19. A method according to claim 18, wherein each spinneret produces an individual jet stream of said conducting fluid.

20. A method according to claim 19, wherein the flow characteristics of each individual jet stream is independently controlled.

21. A method according to claim 20, wherein each spinneret has at least one scanning electrode for electrically independently controlling the flow characteristics of each individual jet stream.

22. A method according to claim 21, wherein each spinneret has two pairs of scanning electrodes for electrically controlling the flow characterists of each individual jet stream.

23. A method according to claim 18, wherein at least two spinnerets deliver different conducting fluids.

24. A method according to claim 23, wherein said different conducting fluids refers to different concentrations of polymer, different polymers, different polymer blends, different additives and/or different solvents.

25. An electrospinning apparatus for forming a membrane, comprising:

a conducting fluid introduction device for providing a quantity of conducting fluid containing a polymer, said conducting fluid introduction device comprising a plurality of electrospinning spinnerets for delivering said conducting fluid, said spinnerets being electrically charged at a first potential;

a ground member positioned adjacent said spinnerets and electrically charged at a second potential different from said first potential, thereby establishing an electric field between said spinnerets and said ground member;

a support member disposed between said spinnerets and said ground member and movable to receive conducting fluid from said spinnerets; and

means for controlling the flow characteristics of conducting fluid from at least one spinneret independently from the flow of conducting fluid from another spinneret.

26. An electrospinning apparatus according to claim 25, wherein said means for independently controlling the flow characteristics comprises at least one electrode disposed adjacent each spinneret, each electrode being charged at a potential different from and separate from said first potential.

27. An electrospinning apparatus according to claim 26, wherein each spinneret has two pairs of scanning electrodes for electrically separately directing the flow characteristics of conducting fluid from said spinneret.

28. An electrospinning apparatus according to claim 26, further comprising a probe associated with at least one spinneret, said probe being disposed between said electrode and said ground member, said probe being electrically charged at a potential different from said spinneret and said electrode.

29. An electrospinning apparatus according to claim 25, wherein said means for independently controlling said flow characteristics comprises a means for individually electrically turning on and off a respective spinneret.

30. An electrospinning apparatus according to claim 29, wherein said means for individually electrically turning on and off a respective spinneret comprises at least one scanning electrode associated with each spinneret.

31. An electrospinning apparatus according to claim 25, wherein said means for independently controlling said flow characteristics comprises a means for applying an alternating gradient to said conducting fluid delivered from said spinnerets.

32. An electrospinning apparatus according to claim 31, wherein said means for applying said alternating gradient comprises a plurality of pairs of electrostatic quadropole lenses.

33. An electrospinning apparatus according to claim 25, wherein said apparatus further comprises a pump for supplying conducting fluid to said solution introduction device at a predetermined pressure.

34. An electrospinning apparatus according to claim 33, wherein said pump is adapted to control the supply rate of conductive fluid at a constant flow rate.

35. An electrospinning apparatus according to claim 33, wherein said pump is adapted to control the supply of conductive fluid at a constant pressure.

36. An electrospinning apparatus according to claim 25, wherein said apparatus comprises a pump system for supplying different conducting fluids to at least two individual spinnerets.

37. An electrospinning apparatus according to claim 25, wherein said solution introduction device comprises a slit-die defining said plurality of spinneret.

38. An electrospinning apparatus according to claim 37, wherein adjacent spinnemets are interconnected by slits.

39. An electrospinning apparatus according to claim 38, wherein said spinnerets are defining by openings in said slit-die and said slits interconnecting said spinnerets are of configurations smaller than said openings.

40. An electrospinning apparatus according to claim 37, further comprising a plurality of scanning electrodes disposed adjacent to each of said spinnerets.

41. An electrospinning apparatus according to claim 25, wherein said solution introduction device comprises a matrix defining said plurality of spinnerets, said spinnerets being disposed in said matrix in electrical isolation from each other.

42. An electrospinning apparatus according to claim 41, wherein at least two individual spinnerets are electrically charged to a different potential.

43. An electrospinning apparatus according to claim 41, further comprising a plurality of individual electrodes wherein at least one individual electrode is disposed adjacent to each individual spinneret.

44. An electrospinning apparatus according to claim 43, wherein at least two of said individual electrodes are electrically charged to a different potential.

45. In an electrospinning apparatus for forming a membrane by electrospinning a plurality of polymer fibers from a conducting fluid which contains a polymer in the presence of an electric field between a conducting fluid introduction device and a ground source, an improved solution introduction device comprising:

a plurality of spinnerets, each for independently delivering a controlled quantity of conducting fluid at a constant pressure or constant flow rate, said spinnerets being charged at an electric potential and being disposed relative to each other to normally interfere with the electric field produced by adjacent spinnerets, each of said spinnerets having a tip at which conducting fluid exits configured to have an electrostatic field strength at each tip stronger than the liquid surface tension at each of said tips.

46. An improved solution introduction device according to claim 45, wherein each spinneret tip is configured by having a selected geometric profile, a selected spatial relationship relative to other spinneret tips or a combination of both.

47. An improved solution introduction device according to claim 46, further comprising an electrode associated with each spinneret configured to produce an electrical potential to at least partially screen electric field interference from adjacent spinnerets.

48. An improved solution introduction device according to claim 45, further comprising a means for at least partially shielding each spinneret tip from electric field interference from adjacent spinnerets.

49. An improved solution introduction device according to claim 48, wherein said means for at least partially shielding is a physical barrier disposed between adjacent spinnerets.

50. An improved solution introduction device according to claim 49, wherein said physical barrier has a conical shape.

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